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Syndrome Characterized by Gynecomastia, Aspermatogenesis without A-Leydigism, and Increased Excretion of Follicle-Stimulating Hormone[1]

[Gynecomastia]

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THE SYNDROME under discussion begins during adolescence and is characterized by gynecomastia and a very specific type of hypogonadism. This latter is almost entirely in respect to the function of the tubular tissue (germinal epithelium and Sertoli cells) while the function of the Leydig cells (growth of phallus and prostate and of sexual hair) remains relatively normal. Thus one finds bilateral gynecomastia, small testes, aspermatogenesis, evidence of normal to moderately reduced function of the Leydig cells, increased excretion of follicle-stimulating hormone (FSH), and usually a reduced excretion of 17-ketosteroids. During the last 4 years, 7 cases have been observed in the clinics of the Massachusetts General Hospital; studies on these patients and two additional private patients form the subject of this report.

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REVIEW OF LITERATURE

Although these cases are not uncommon, few reports are found in the literature, and to our knowledge, no author has grouped them together as a definite clinical entity. Bedor in 1812, according to a later writer (1), described two brothers, 21 and 24 years old, with bilateral gynecomastia and small testes. Around 1840, several English authors (2–5) independently described a soldier, previously normal, who at the age of 53, developed small testes and gynecomastia a few months after trauma to the testes. The reports of this case vary in their details but the sequence of events seems to have been as stated. The development of gynecomastia in a previously normal 22-year-old patient a few months after mumps orchitis was reported in 1877 (1). During the last 20 years, there have been several reports (5–9) of cases which possibly fit into this syndrome. Bronstein (10) in 1939 reported the only case, however, in which those hormone studies necessary for the diagnosis were carried out. This concerned a 17-year-old negro with gynecomastia of 5 years' duration. The testes were very small and there was azo-

öspermia. The phallus was normal, while the other accessory sex organs were small; the amount and distribution of the pubic and axillary hair were normal; the span was 10.5 cm. greater than the height. Estrin excretion was not increased while that of gonadotropin was. The adrenals were normal as shown by roentgenograms after perirenal air injection; the sella turcica was not enlarged. The author did not believe that the gynecomastia was due to hyperestrinism and suggested a pituitary origin.

Other Causes of Gynecomastia

During puberty, nearly all boys have some breast enlargement (11). Usually slight and often unnoticed, it recedes rapidly as a rule but may become so great as to require excision. Strangely enough, the enlargement may increase on one side and regress on the other, often without apparent cause, although trauma is thought to be an important factor.

Gynecomastia is frequently found in association with testicular tumors. Gilbert (12) has recently subdivided these cases into 'choriogenic' and 'physiologic' types. In the former, which occurs with chorionepitheliomata, the breasts may secrete; the areolae are enlarged and pigmented; the estrin and gonadotropin titers of the urine are very high. The gynecomastia is presumably caused by the estrin secreted by the tumor. 'Physiologic' gynecomastia, on the other hand, occurs with other testicular tumors, such as seminomata, teratomata and interstitial cell tumors. In this type, the breasts do not secrete, the areolae are not enlarged or pigmented, and the gonadotropin titer of the urine is only moderately increased. This form of gynecomastia is presumably secondary to atrophy of the remaining testis, as it frequently occurs after roentgen ray treatment has been given post-operatively (13, 14). It is probably related to the syndrome under discussion (*vide infra*).

Adrenal cortical tumors of the so-called 'feminizing type' cause gynecomastia (15). With the breast enlargement, there is loss of libido, decrease in secondary sex characteristics, and testicular atrophy. In one case, large quantities of estrin were found in the urine (16); it is quite possible that hyperestrinism is the cause of the gynecomastia in this condition.

Gynecomastia not infrequently occurs with cirrhosis of the liver. Glass, Edmondson, and Soll (17) found atrophic testes in all of their cases and an increased partition of free estrin as opposed to conjugated estrin in the urine. They believe that the cause of the gynecomastia is hyperestrinism, secondary to failure of the liver to properly metabolize estrin. No testicular biopsies were made in their cases.

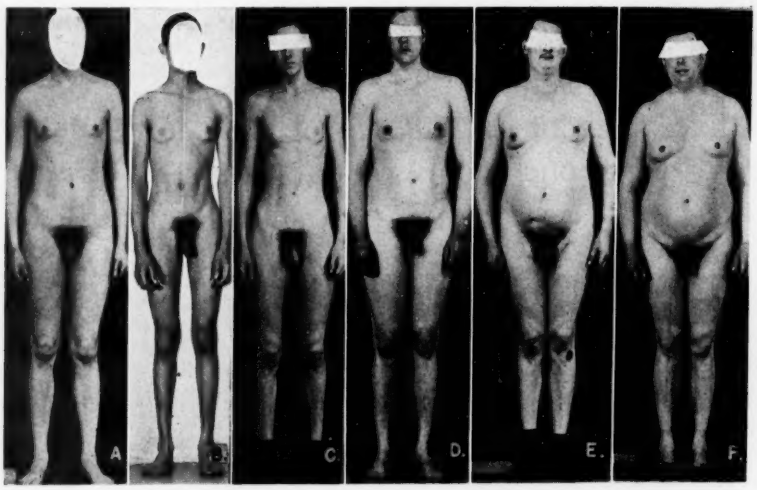

Fig. 1. Masculine body configurations and relatively normal development of the accessory sexual organs, except for the breasts. *A, case 1; B, case 2; C, case 3; D, case 6; E, case 8; F, case 9.*

Gynecomastia rarely occurs with pituitary tumors (18, 19), hyperthyroidism (20) and after prostatectomy (21).

Clinical Findings

The 9 cases here reported whose histories are outlined in the appendix varied in age from 17 to 38 years; all were white except one negro. Three had an asthenic habitus; 4 were somewhat obese; 2 had a normal build. All of the patients were strong and had good muscular development (fig. 1).

Early development was normal in every case. None of the patients had undescended testes. There was no history of orchitis, although most of the patients had had mumps. Puberty started between the ages of 12 and 14 in each case.

The gynecomastia was bilateral in every case; (fig. 2 and 3); it was first noticed by the patients from

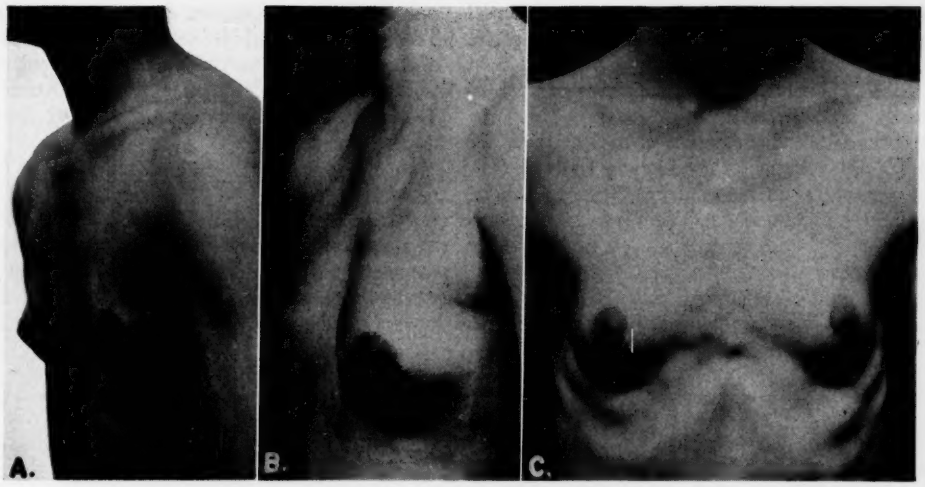

Fig. 2. *A, case 2; B, case 6; C, case 3.*

1 to 6 years after puberty began. Those patients who observed breast enlargement during the first few years after the onset of puberty stated that the breasts slowly increased in size over a period of several years and then remained stationary; those who did not notice the enlargement until 4 to 6 years after the onset of puberty, on the other hand, said that there was no further change during the subsequent years. The gynecomastia was marked in 7 cases and moderate in 2. The breasts resembled those of the adolescent female, with some areolar enlargement and very little increase in pigmentation. No secretion was expressed in any case, and in only two cases was tenderness present. This was unilateral and started after manual stimulation in one case.

The testes were very small, measuring about 1.5 ×1.0×0.5 cm. There was no difference between the two sides and there was very little variation among cases. The testes were normal as to firmness and sensitivity to pressure. Those patients who had observed the size of their testes stated that they had always been small.

Three of the patients had no semen, i.e., aspermia while the remaining 6 had ejaculations. Semen examination showed azoöspermia in the 4 cases in which this test was made. Sterility was the chief complaint of 3 patients.

Eight of the 9 cases had well developed accessory sexual organs, and clinically all 8 patients had relatively good Leydig function, although the younger patients appeared immature for their age. Only *case 5* had obviously diminished Leydig function. He, at the age of 28, had a high-pitched voice, a small larynx, sparse beard, small phallus and small prostate. He had

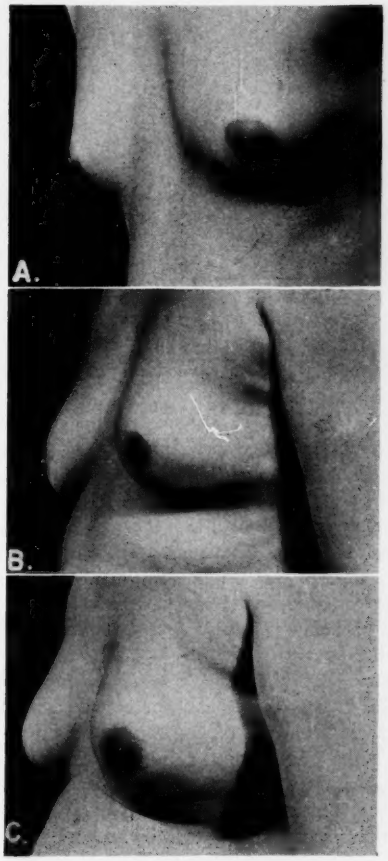

Fig. 3. *A, case 1; B, case 8; C, case 9.*

erections but no ejaculations and never attempted intercourse, although he was attracted to the opposite sex.

Axillary, pubic and perianal hair growth were essentially normal in these patients, and several of the older ones had definite recession of the hair above the temples, an indication of good Leydig function (22). The 5 younger patients, aged 17, 18, 22, 24, and 28, respectively, did not shave. Two of the 4 older ones had scanty beards localized to the chin and upper lip which required shaving only once or twice a week. In one patient, however, this was a familial characteristic. Body hair was scanty in all of the 7 patients and showed no consistent deviation from normal. There was no clinical evidence of liver disease in any of the patients; in *cases 2* and *5*, the bromsulphalein test, the cephalin flocculation test, the serum Van den Bergh reaction, the serum proteins, and the A/G ratios were normal.

Hormonal Findings

Follicle-stimulating hormone. All of the patients excreted excessive amounts of the pituitary follicle-stimulating hormone (FSH) in the urine. By our assay method (23), which is a modification of the alcohol precipitation method of Zondek, a normal male rarely

TABLE 1. CLINICAL DATA ON PATIENTS WITH GYNECOMASTIA

Case no.	Age, yr.	Onset of Puberty, yr.	Gynecomastia First Noted, age,	Bone Age, yr.	Height, cm.	Span, cm.	Highest FSH Determinations				17-Ketosteroids, mg./24 hr.			Remarks
							Mouse Units/100 cc.		Mouse Units/24 hr.					
							Greater than	Less than	Greater than	Less than	Low	High	Ave.	
1	17	13	13	Normal	181.1	185.0	30	50	235	350	5.6	8.7	7.2	
2	18	14	14	Normal	170.7	180.2	100	150	640	840			*	Negro
3	22	14	17	Normal	175.4	178.0	50	80	150	248	6.0	9.0	7.2	
4	24	14	18	Normal	182.2	183.5	80	100			1 Assay		4.8	Hysteria
5	28	14	18	Delayed	177.0	181.5	50	100			3.9	5.2	4.6	Definite hypoleydigism
6	30	13	14	Normal	183.5	184.2	50	80	200	320	12.6	13.5	13.1	Narcolepsy. Renal lithiasis
7	33	13	16		182.2	184.2	30	50	270	450	7.2	13.2	9.6	
8	35	14	16	Normal	177.5	178.0	30	50	330	455	9.6	11.2	10.3	
9	38	12	18		171.6	175.5	50	80			7.9	10.5	9.2	Chronic cystic disease of right lung

* The pre-treatment assays of 1.2 and 2.4 mg. averaging 1.8 mg. per 24 hr. are thought to be due to faulty technique, and are not included. Later assays, after 4 to 6 weeks without treatment, ranged from 4.3 to 9.0 mg., with an average of 5.7 mg. per 24 hr.

with abnormal beards while the 2 with heavy beards had abundant body hair.

Bone age (table 1) was determined in all of the younger patients and was definitely delayed in only one patient, *case 5*. At the age of 21 the epiphyses of the radius and ulna were open, indicating a delay of 3 years in bone age; however, at the age of 28, without treatment, these epiphyses were closed. The span exceeded the height in every case, however; where this discrepancy was marked, circa 4 to 5 cm., there probably had been some delayed epiphyseal union.

There was questionable serological evidence of syphilis in only one patient, *case 2*; the Hinton test was negative in the others. Roentgenograms of the sella turcica were uniformly normal. Perirenal air injections were performed on 2 patients and the findings were normal. Glucose tolerance tests were made on 3 patients and revealed nothing remarkable. Basal metabolic rates were obtained on 6 patients

excretes 10 mouse units of FSH per 100 cc. of concentrated first morning urine. These patients uniformly excreted more than 30 M.U. per 100 cc., and 5 of the 8 have excreted more than 50 M.U. per 100 cc. (table 1). In the table, FSH excretion levels in some cases are also recorded in M.U. per 24 hr. Calculated on this basis, the excretion levels were also much above normal. Such data required very accurate collections of urine which were not obtainable in all cases. These high levels of FSH excretion are comparable to the levels found in castrates and their significance will be discussed later.

17-Ketosteroids. The urinary excretion of 17-ketosteroids varied from relatively normal to definitely subnormal levels. Thus, in a small series of normal males between the ages of 20 and 40, values from 8.1 to 22.6 with an average of 13.8 mg. per 24 hours were obtained in this laboratory (24). As can be seen from the table, the range in this series of 9 patients was from 3.9 to 13.5 with an average of 8.3 mg. per

24 hr. By and large, there was a parallelism between the degree of hypoleydigism, as judged clinically, and the lowering of the 17-ketosteroid excretion.

Estrin assays. Estrin assays were made on *case 2* by Drs. C. V. and O. W. Smith in the Fearing Research Laboratory of the Free Hospital for Women. They found no evidence of increased excretion of either estrin or estrin-breakdown products, the levels being about the same as those found in menopausal women and in the only normal male they had studied. Estrin assay on *case 8* made in our laboratory in 1938 was negative for 10 R.U. per 24 hr.

Histological Findings

Testis. Testicular biopsies were obtained from 7 patients and showed varying degrees of the same lesion. This involved the tubules and in its most advanced state consisted of hyalinization of all the tubular elements (fig. 4, 5). This hyaline tissue stained pink with eosin and like collagen with phosphotungstic acid and aniline blue. Stains for amyloid were negative. In many of the biopsy tissues, fine granules were seen in the hyaline tissue; these granules did not stain like collagen, however, and their nature is obscure; they seem to be part of the atrophic or degenerative process. This lesion of the tubules is not the 'peritubular fibrosis' described by Charny and Meranze (25), and there was no evidence of an inflammatory process in any of the biopsies. The less advanced lesions showed partial hyalinization with impaired spermatogenesis (fig. 4, B); in no instance was normal spermatogenesis present.

The interstitial cells were numerous in all of the biopsies and in most cases the Leydig cells seemed, at first, more numerous than could be accounted for by the atrophy and shrinkage of the seminiferous tubules. Indeed, the diagnosis 'hyperplasia of the interstitial cells' was considered by the pathologist. When one calculates the size of these small testes, however, it seems probable that simple shrinkage can account for the apparent increase in the number of interstitial cells. A testis measuring 1.5×1.0×0.5 cm. equals approximately 0.75 cc. of tissue, while a normal testis measuring 5.0×3.0×2.0 cm. equals approximately 30 cc. of tissue. In other words, one would expect the interstitial cells to be 40 times as numerous as in the normal testis.

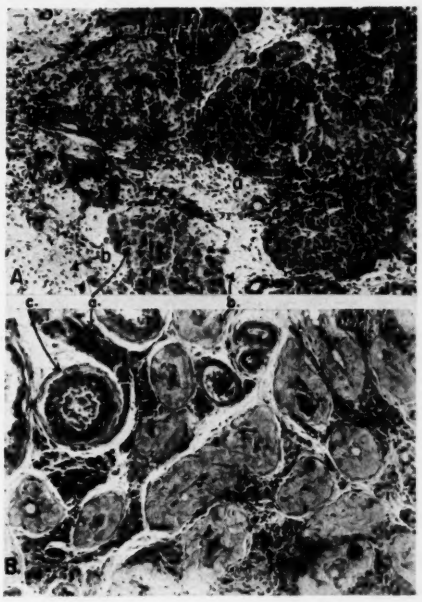

Fig. 4. TESTICULAR BIOPSY TISSUE. A, *case 6;* B, *case 7. a,* Leydig cells; *b,* completely hyalinized tubules; *c,* partially hyalinized tubule. Note that the Leydig cells in A almost suggest adenoma formation.

Breast. The breast tissue was examined microscopically in 4 patients and showed some hyperplasia of the duct epithelium and marked proliferation of the periductal connective tissue (fig. 6, A and B.). These findings are definitely different from the effects produced by estrin therapy in an elderly male (fig. 6, C); there the ratio of ductal to periductal hyperplasia was greater.

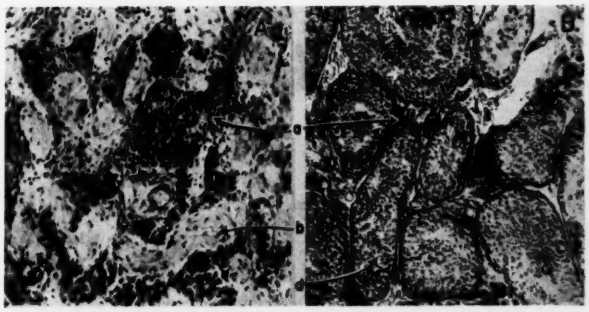

Fig. 5. TESTICULAR BIOPSY TISSUE. A, *case 1;* B, normal. *a,* Leydig cells; *b,* completely hyalinized tubule; *d,* normal tubule.

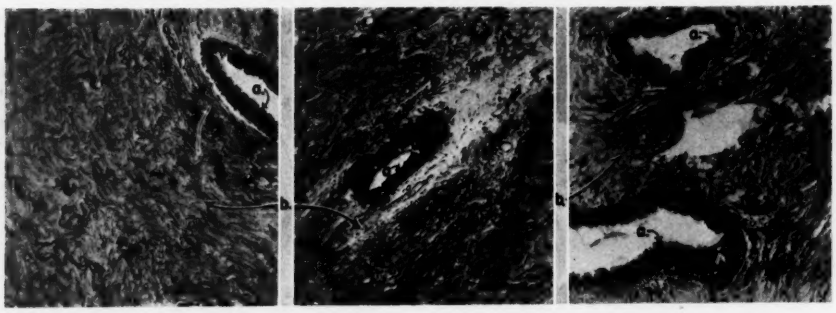

Fig. 6. BREAST TISSUE. *A, case 2; B, case 6; C, M. G. H. 334479,* a 78-year-old male with estrin-induced gynecomastia. In A and B there is only moderate ductal hyperplasia (*a*), with marked proliferation of the periductal connective tissue (*b*); in C, the ductal hyperplasia (*a*) is more marked and the periductal connective tissue (*b*) is less dense.

Pathological Physiology

Significance of increased FSH excretion. Since the significance of an increased FSH excretion has been more thoroughly studied in the female, it may be well for purposes of orientation to consider first the hormonal patterns in the normal and in the gonadectomized female. In figure 7, A the part of the anterior pituitary under consideration is divided into 2 compartments, one for FSH and one for the luteinizing hormone (LH). In this and subsequent diagrams, stimulating influences are indicated by arrows with solid heads while inhibiting influences are indicated by arrows with open heads. It will be noted that FSH stimulates the ovary to produce estrin (E); that estrin in turn inhibits FSH production and stimulates LH production. The evidence for these statements is discussed in a previous paper (26). To be absolutely accurate it is still a question whether estrin stimulates LH or luteotropin or both; this uncertainty is indicated by the question mark after LH in the second compartment. For the present argument this is immaterial. The important fact is that estrin stimulates some hormone of the pituitary which in turn stimulates the ovary to produce more progestin (P). Finally, it will be noted that progestin inhibits LH production (27).

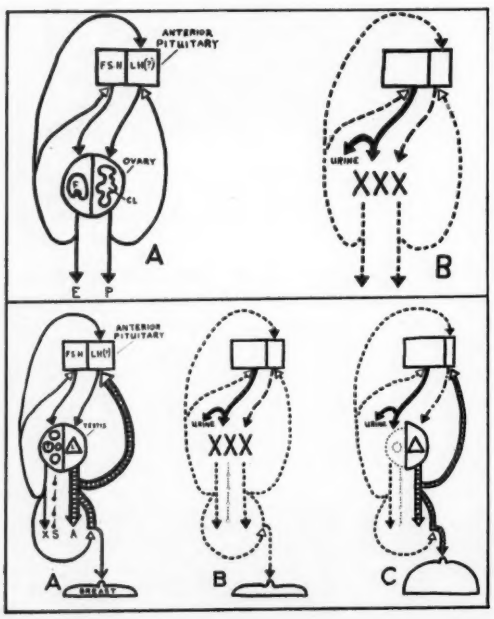

Fig. 7. SCHEMATIC DRAWING REPRESENTING HORMONAL PATTERNS in normal female (A) and gonadectomized female (B). Finely dotted line indicates absence of hormone; broken line indicates decreased production of hormone. For discussion, see text.

Fig. 8. SCHEMATIC DRAWING REPRESENTING HORMONAL PATTERNS in normal male (A), gonadectomized male (B), and syndrome under discussion (C). Finely dotted line indicates absence of hormone; dot-dash line indicates markedly decreased production of hormone; broken line indicates decreased production of hormone. For discussion, see text.

Figure 7, B is constructed in a similar manner to show the changes in the hormonal pattern resulting from castration. Estrin is absent and consequently there is no inhibition of FSH production. There results an overproduction of FSH and large quantities are excreted in the urine. It will be noted that LH production is depicted as decreased. Whether this is true in the gonadectomized female probably depends on whether the loss of the stimulating effect of estrin on LH overbalances the loss of the inhibiting effect of progestin on LH.

Before describing the hormonal pattern in the syndrome under discussion (fig. 8, C) it will be helpful to outline these patterns in the normal and in the gonadectomized male (fig. 8, A and B). These diagrams follow the same general scheme as those in figure 7. It will be noted that FSH stimulates the tubules (T) to produce spermatozoa (S) (28) and an 'X-hormone.' The arguments for the existence of this X-hormone and for its actions will be enumerated

below. It will be noted further that the X-hormone is analogous to estrin in that it inhibits FSH production and stimulates LH production. LH stimulates the Leydig cells (L) to produce androgen (A) (28); androgen, like progestin, inhibits LH production. The discussion of the effect of these various hormones on the breast is reserved for a later section.

In figure 8, B it should be emphasized that it is primarily lack of the inhibiting effect of the X-hormone on FSH, and not lack of androgen, that leads to overproduction of FSH. The situation, therefore, is depicted as exactly analogous to that in a gonadectomized female; the arguments for this rendering will be discussed below.

Turning to the hormonal pattern of the syndrome under discussion (fig. 8, C) one notes first that the tubular part of the testis is non-functioning while the part which has to do with Leydig cells is relatively normal (cf. biopsies, fig. 4, 5). The increased FSH production is the result of lack of X-hormone with its inhibiting effect. LH production is less than normal because of lack of stimulation by the X-hormone; it is even less than that in the male castrate (fig. 8, B) because the inhibiting effect of androgen is partially retained. Androgen production, while less than normal, is still present.

The description of the hormonal pattern has been expressed in rather dogmatic terms. The argument will now be taken up point by point.

Evidence for a second or X-hormone (inhibin) of the testis. The first and weakest argument for the presence of a second testicular hormone is by analogy with the female. There FSH facilitates production not only of the germ cells but of a hormone, estrin, as well; it would seem, therefore, in the male that FSH might be concerned with the production of a hormone in addition to the germ cells.

The literature, furthermore, contains considerable evidence in favor of the existence of such a hormone. Mottram and Cramer (29) in 1923 found castration cells in the pituitaries of adult male rats that had received roentgen ray treatment to the testes. This treatment resulted in atrophy of the seminiferous tubules but preservation of the interstitial cells and accessory sex organs. Witschi, Levine and Hill (30) in 1932 found that female rats in parabiosis with such male rats develop continuous estrus. This finding is good evidence for increased FSH production. Martins and Rocha (31) in 1931 reported on parabiotic union of castrated males with infantile normal females. When the males were untreated, precocious puberty resulted in the females; however, when the males were treated with testicular extracts or implants, precocious puberty did not occur in the females, in spite of the fact that the extracts did not contain androgen as judged by the accessory sex organs of the treated males. McCullagh and Walsh (32) confirmed this work and coined the word 'inhibin' for the water-soluble, non-androgenic hormone of the testis. They showed furthermore that inhibin caused regression of the prostate and seminal vesicles in normal rats. This finding was confirmed by Vidgoff, Hill, Vehrs, and Kubin (33) in 1939 and brings to mind Huggins' studies (34) on the effect of estrin (a hormone closely related to inhibin) on the prostates of dogs. Nelson (35) in 1934 studied rats made cryptorchid by operation and found castration cells in the pituitaries after 75 days, while 240 days were required for atrophy of the seminal vesicles and 400 days for the prostate. Since the tubules in cryptorchid males degenerate long before the interstitial cells, these time relationships suggest that the occurrence of castration cells is correlated with the tubules while the atrophy of the seminal vesicles and prostate is correlated with the interstitial cells. Indeed, the atrophy of the interstitial cells may very well be due to lack of stimulation of LH by inhibin (fig. 8, A). There are, of course, other interpretations (*vide infra*).

The clinical findings in certain cases of arrhenoblastoma of the ovary suggest that these tumors produce some hormone other than androgen. Thus, in one (*M.G.H. 176118*) of the 4 cases studied in this clinic there were no masculinizing effects, merely amenorrhea. The amenorrhea in this case disappeared shortly after removal of the tumor. Although complete hormonal studies are lacking, it would seem in retrospect that the finding could best be explained on the supposition that the tumor in this case primarily produced inhibin. Indeed, in the 2 cases with definitely masculinizing symptoms, (*M.G.H. 174195* and *245129*) the 17-ketosteroid excretion levels were not elevated which suggests that even in these cases the amenorrhea might have resulted from excessive production of inhibin.

The authors believe that the findings in the syndrome here described offer strong evidence in favor of the dual hormonal theory of testis physiology. Here nature has apparently produced destruction of one part of the testis while sparing the other. In the face of only slight if any hypoleydigism, one encounters FSH excretion of the order of magnitude of that found in castrates. Thus *case 6*, with perfectly normal development of the accessory sexual organs, aside from the gynecomastia, and with a relatively normal 17-ketosteroid output, excreted more than 200 M.U. of FSH per 24 hours. Furthermore, the very fact that gynecomastia occurs in this syndrome while it does not occur after castration is further evidence that some hormone other than androgen is involved.

Evidence against a second or X-hormone of the testis. The fact that testosterone inhibits FSH pro-

duction has led to an alternate theory, the monohormonal theory. Thus, Nelson (35) points out that the sequellae of experimental cryptorchidism in rats discussed above disappear under testosterone therapy in the reverse order in which they occur, and thinks that everything can be explained on the basis of dosages. If this interpretation were extended to the syndrome here presented, the argument would be that the patients were suffering from a mild degree of hypoleydigism, not sufficient to affect the genital organs but sufficient to cause increased FSH production. A point perhaps against this argument is that *case 2* with the highest FSH excretion did not have the greatest degree of hypoleydigism.

In rebuttal, the authors point out that the histological picture of hyalinized tubules in the presence of normal or hypertrophic interstitial cells make it difficult to believe that one is dealing primarily with an underfunction of the androgen-producing elements. Moreover, the fact that so much more testosterone is required to prevent development of castration cells than to affect seminal vesicles and prostate suggest to the authors that inhibition of formation of castration cells is not a physiological function of testosterone. It seems not impossible to the authors, furthermore, that the inhibitory effect of testosterone on FSH production may very well be connected with the observation that if testosterone is administered to eunuchoids and castrated females, the excretion of estrin is increased (36–39). It is very possible that testosterone is converted into estrin which inhibits FSH.

Cause of the decreased 17-ketosteroid excretion. The 17-ketosteroids in the male are produced in two places, the adrenal cortex and the cells of Leydig (24). In the syndrome here described the values vary from apparently normal to definitely subnormal. Since the 17-ketosteroid excretion level varies considerably among normal individuals it can not be said that any one of the patients here reported had an excretion level as high as it would have been without the disease. The authors suggest, as an explanation for this lowering, a lack of X-hormone to stimulate both the Leydig cells and possibly those cells of the adrenal cortex which produce 17-ketosteroids. The above chain is thoroughly discussed in the paper previously referred to (26).

Cause of the gynecomastia. The most puzzling part of the whole syndrome is the gynecomastia. One first considers the possibility of too much estrin. Against this possibility are *a*), the presence of high FSH excretion, *b*), the fact that the histological changes in the breast are more periductal than ductal hyperplasia, and *c*), the fact that no increased estrin excretion was found in *case 2* by Drs. G. V. and O. W. Smith or in *case 8* in our laboratory.

One might consider the uncommon causes of gynecomastia such as adrenal hyperfunction, pituitary tumors and testicular tumors. No evidence in favor of these has been found. Progesterone was administered to *cases 1* and *2* with the thought that this would be followed by lactation if excess of prolactin had anything to do with the etiology. Lactation did not occur.

Could the gynecomastia be due to testosterone? It has been shown that testosterone stimulates breast tissue in normal and castrated female and male rats (40). Gynecomastia is not uncommon in eunuchoid patients treated with testosterone (41); it became so marked in one of our patients as to require excision. The excised breasts in this particular case showed the same histological picture seen in this syndrome. But testosterone can not be the only factor, since if this were so, normal males would have gynecomastia.

After all, the pathology indicates isoleydigism accompanied by hypoinhibinism. The authors bring up for discussion the hypothesis that for the production of this type of gynecomastia, two conditions must be fulfilled. *a*), presence of androgen, *b*), absence of inhibin. One is reminded of Huggins' observations on the prostate of dogs in which he found that testosterone causes growth and estrin prevents such growth (34). Could it not be that in the male breast testosterone causes growth and inhibin prevents this growth? If such were the case the castrate would not develop gynecomastia because of the lack of testosterone (fig. 8, B), the normal would not because of the presence of inhibin (fig. 8, A), while the patients with this syndrome would, since they have testosterone but no inhibin (fig. 8, C). To be sure, Hamilton (42) has found that testosterone therapy does not always cause gynecomastia in male castrates. Since these cases were all adults, it may very well be that a third condition need be fulfilled, namely that the patient be growing at the time of the hormonal imbalance.

To recapitulate, the selective lesion of the seminiferous tubules results not only in aspermatogenesis but also in lack of X-hormone (inhibin); lack of X-hormone leads not only to increased FSH production but to decreased LH production as well; consequently the intact Leydig cells produce somewhat less androgen than normally; the androgen produced acts on the breast during puberty in the absence of X-hormone to cause gynecomastia.

Etiology

Nothing has been found in these patients to explain the testicular lesion. There is no evidence of any inflammatory disease clinically or histologically. An obstructive lesion of the vas deferens seems most

unlikely since histological studies of the testes in cases of known obstruction do not resemble at all the histological picture seen here (43). Furthermore an epididymal biopsy from *case 6* contained normal tissue. The changes, moreover, are not those seen with lack of gonadotropic hormones, as in pituitary dwarfs in which one finds rudimentary tubules with aspermatogenesis but no hyalinization. One is left with the conclusion that the lesion is a degenerative one of unknown etiology, starting early in life.

Treatment

It is very improbable that the gynceomastia is reversible. Testosterone propionate and progesterone have been tried without success; estradiol dipropionate caused further enlargement. Surgical removal of the breast is recommended for cosmetic reasons, and if carefully done is an exceedingly satisfactory procedure.

From the histological findings, it seems unlikely that anything can be done to correct the aspermatogenesis. The high FSH titers in the urine demonstrate that these patients are over-producing FSH in an effort to stimulate spermatogenesis. Therefore, therapy with gonadotropins is probably illogical.

For those patients in this group who are suffering from hypoleydigism, testosterone therapy is probably indicated. Chorionic gonadotropin therapy by stimulating the interstitial cells might conceivably be used to produce the same results as testosterone; it has not been tried by the authors in the series of cases here reported.

SUMMARY OF FACTS

1. Nine cases are presented of a syndrome characterized by gynecomastia, and small testes with aspermatogenesis but without a-leydigism.

2. The follicle-stimulating hormone (FSH) excretion in the urine is increased to a degree comparable to that found in castrates.

3. Estrin excretion was studied in two cases and found not to be increased.

4. The 17-ketosteroid excretion level and the development of the accessory sexual organs vary from apparently normal to definitely subnormal.

5. Testicular biopsies were obtained on 7 patients and showed hyalinization of the seminiferous tubules and normal appearing interstitial cells.

6. Breast tissue was examined on 4 patients and showed some ductal hyperplasia with marked proliferation of the periductal connective tissue.

Interpretations

1. These studies support the point of view that the testis produces two hormones; *a*), androgen from the Leydig cells, and *b*), X-hormone (inhibin) from the tubules.

2. Inhibin is analogous and probably very similar to estrin.

3. The increased FSH excretion which is found in certain types of hypogonadism depends primarily upon lack of inhibin and only to a lesser degree upon lack of androgen; indeed the action of testosterone in inhibiting FSH may depend upon its conversion into estrin.

4. The gynecomastia is not due to hyperestrinism; it is not due to androgen alone; it may be due to the combination of androgen and lack of inhibin.

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CASE HISTORIES

In the following case abstracts, the data for the FSH tests and the 17-ketosteroid excretion levels are omitted, as they are recorded in table 1.

Case 1 (fig. 1, A), *R.R.* (*M.G.H. 344755*), a 17-year-old white schoolboy, was seen in March, 1942, complaining that he had been rejected by the Navy because of small testes. His general health was excellent. He had mumps at 2 years of age without orchitis. At 10 or 11, he suffered from trauma of the scrotum, but there was no swelling or pain. Since that time, he noticed that the testes were small. Puberty began at 13 and progressed normally. He had normal erections, masturbated occasionally, but had no ejaculations or nocturnal emissions. He never shaved, but his voice had changed. Shortly after the onset of puberty, he noted enlargement of the breasts which slowly increased for a few years (fig. 3, A). The enlargement was never enough to cause him embarrassment.

Examination showed a well developed, muscular boy with mild acne, with somewhat narrow shoulders and rather wide hips. The span was 4.0 cm. greater than the height. Axillary and facial hair were scanty, but pubic hair was normal. The voice was deep and the larynx showed normal masculine enlargement. The breasts were moderately and equally enlarged, non-tender, and no secretion could be expressed. The phallus and scrotum were well developed; the prostate was slightly small. The testes were very small, equal in size, firm and normally sensitive.

Hinton test for syphilis was negative. Roentgenograms showed a normal bone age. Biopsy of the right testis showed complete hyalinization of the tubules and apparently normal interstitial cells (fig. 5, A). Estradiol dipropionate, 5 mg. intramuscularly every 5 days, caused tenderness and further enlargement of both breasts after 4 injections.

Case 2 (fig. 1, B), *G.B.* (*M.G.H. 147829*), an 18-year-old negro, was admitted in September, 1941, complaining of gynecomastia. His general health was always good; early development was normal. He had measles, chicken

pox, scarlet fever and pneumonia in childhood, but not mumps. At the age of 10, he was seen in another hospital because of a coarse tremor of both hands. Wassermann reaction and Kolmer tests were positive, while the Kahn test was negative. He received no antisyphilitic treatment, and the tremor ceased after a few weeks. Five and 7 years later, Hinton tests were negative; there was never any clinical evidence of syphilis. He had never had orchitis or testicular trauma, and had never noticed the size of the testes. Puberty began at 14 and progressed fairly normally. He masturbated occasionally with pleasurable sensation, but without ejaculations; he had erections but no nocturnal emissions. Within a year of the onset of puberty, he noticed enlargement of the breasts and this increased slowly during the next few years (fig. 2, A).

Examination showed a well developed, thin boy who appeared younger than his stated age. The span was 9.5 cm. greater than the height. Axillary, pubic and perianal hair were normal; he had no beard. The voice was deep and the larynx was normal in size. The breasts were quite large, resembling those of a pubertal girl, non-tender and no secretion could be expressed. The phallus was quite large; the scrotum was well developed; the prostate about normal in size. The testes were extremely small and equal in size. There was a small hydrocele on the right.

Hinton test was negative on three occasions and doubtful on one. Estrin essays: 15 R.U./24 hr. (equivalent to 7.5 micrograms of estrone/24 hr.) before zinc hydrolysis; 42 R.U./24 hr. after zinc hydrolysis (Drs. G. V. and O. W. Smith). The bromsulphalein, cephalin flocculation and Van den Bergh tests were all normal, as was the serum protein content of the blood. Glucose and insulin tolerance tests were entirely normal. Roentgen-ray examination showed a normal sella turcica, normal bone age, and normal adrenals after air injection. Biopsy of the right testis showed marked impairment of spermatogenesis with hyalinization of many seminiferous tubules while the interstitial cells were well preserved.

This patient was treated with large doses of testosterone propionate, progesterone, and pregnenolone without grossly altering the breasts or testes. In June, 1942, both breasts were excised and showed proliferation of the ductal epithelium with marked proliferation of the periductal connective tissue (fig. 6, A). Hinton test was again negative.

Case 3 (fig. 1, C), *F.S.* (*M.G.H. 119837*), a 22-year-old single white laborer, was seen in March, 1940, complaining of gynecomastia. His general health was always fairly good, but he had always been thin. He had mumps without orchitis. There was no history of any previous disease of the testes; the patient thought they were 'always small.' At 13, he had an operation on the left eye for strabismus. For many years he had had severe dental caries and pyorrhea. Puberty began at 14 and progressed normally. At 17 he first noticed enlargement of the breasts and this increased slowly for several years (fig. 2, C). There was no further enlargement during the 2 years that he was under observation. He had satisfactory erections, intercourse and ejaculations.

Examination showed a tall, thin man with large hands and feet who appeared younger than the stated age. The span was 2.5 cm. greater than the height. Axillary and pubic hair was normal, but the beard was scanty. The voice was a little high-pitched, but the larynx was of normal size. The breasts were markedly enlarged, resembling those of an adolescent girl; they were not tender and no secretion could be expressed. The phallus, prostate, and scrotum were normally developed. The testes were extremely small, but the epididymes were well developed.

Hinton test was negative. Biopsy of the left testis showed complete hyalinization of the seminiferous tubules and normal looking interstitial cells. This patient was treated for several months with large doses of testosterone propionate without any effect on the breasts or testes.

Case 4, *B.C.*, (private patient of Dr. J. O. W. Rash), a 24-year-old unmarried white laborer, complained of gynecomastia and small testes. He was always robust and was somewhat obese from the age of 10 to 15 years. He had measles at 9 and influenza 3 or 4 times in childhood. There was no history of mumps orchitis, or trauma to the testes. From 8 to 12, he had frequent attacks of syncope, with loss of memory, lasting 30 to 45 minutes, without epileptiform symptoms. Puberty began at 12 and progressed fairly normally, except that the voice never changed and he had never shaved. Intercourse was unsatisfactory; he had ejaculations, but no nocturnal emissions. Glasses were prescribed at 10 because of poor vision in the right eye; at 17 he complained of increased loss of vision with blurring and was admitted to the Johns Hopkins Hospital. It was noted then that he had gynecomastia and small testes. Ventriculograms revealed no abnormality; visual fields showed a binasal hemianopsia, which was thought to be functional in origin. The gynecomastia was first noticed by the patient at the age of 18 and has not progressed since that time.

Examination showed a rather obese, unintelligent, timid, self-conscious man with wide hips and slightly narrow shoulders. The span was not significantly greater than the height. The axillary and perianal hair were scanty; the pubic hair was normal; the beard was scanty. The voice was high-pitched. There was complete loss of vision in the right nasal quadrants; the optic fundi were normal. The breasts were greatly enlarged. The phallus was normal in size, with a slight degree of hypospadias; the prostate was somewhat small. The testes were very small, equal in size and normal in consistency. Roentgenograms showed a normal bone age. No semen specimen or testicular biopsy could be obtained.

Case 5, *W.J.* (*M.G.H. 296608*), a 28-year-old feeble-minded white houseboy was admitted in April, 1934, at the age of 21 because of gynecomastia. He was an inmate of a State Institution and during the few months before admission manual manipulaton resulted in swelling and pain of the right breast. His general health was fairly good. He had had influenza on two occasions, but did not remember having mumps. He never had orchitis or trauma to the testes, and thought the testes were 'always small.' Puberty began at 15, but the voice did not change, and he never had nocturnal emissions. He had erections but never attempted intercourse and masturbated only a few times, with no ejaculations. At about 18, he first noticed

breast enlargement and this continued for the next few years. The breasts were never painful or tender until the months before admission (*vide supra*).

Examination showed a tall immature boy with narrow sloping shoulders and wide hips. The height was 2.0 cm. greater than the span. Axillary and pubic hair were normal; the voice was high-pitched. Both breasts were markedly enlarged, the right more than the left; the right breast was slightly tender to palpation. The phallus and scrotum were fairly well developed while the prostate was small. The testes were very small.

The FSH test was positive for at least 8 M.U. per 100 cc. The glucose tolerance test was not remarkable. Roentgenograms showed a normal sella turcica; the epiphyses of the radius and ulna were open, indicating a 3-year delay in bone age. Basal metabolic determinations were −4, −5 and +9. Both breasts were amputated and showed hyperplasia of the ductal epithelium and proliferation of the periductal connective tissue.

The patient was again seen in November, 1941, at the age of 28. The voice had not changed and he had not shaved. He had only occasional erections, no ejaculations and had not attempted intercourse.

Examination showed a tall, immature boy who was quite thin. The span was 5.0 cm. greater than the height. Axillary and pubic hair were normal; facial hair was sparse. The voice was high-pitched and the larynx did not show normal masculine development. No breast tissue could be felt under the scars of the amputations. The phallus and scrotum were still only fairly well developed and the prostate was small. The testes were extremely small. There was a hydrocele on the left.

Hinton test was negative. Roentgenograms showed that the epiphyses of the radius and ulna had closed. The bromsulphalein, cephalin flocculation, and Van den Bergh tests were normal, as were the serum proteins. Biopsy of the right testis showed marked impairment of spermatogenesis with hyalinization of most of the tubules and normal appearing interstitial cells.

Case 6 (fig. 1, D), *L.B.* (*M.G.H. 141135*), a 30-year-old unmarried mechanic, was seen in May, 1942, complaining of small testes and gynecomastia. His general health was always good. He had never had mumps and there was no history of orchitis. The testes were 'always small.' At 11 and again at 30, he had pneumonia without complications. Puberty began at 13 and progressed normally. At 14, he first noticed lumps in both breasts which were slightly tender. The breasts slowly increased in size, and he could not remember when they ceased enlarging, but they had remained stationary for at least 6 years (fig. 2, B). At 28, he received testosterone propionate, 25 mg. intramuscularly 3 times weekly because of soreness of the left breast; this caused no change in the size of the breasts but the soreness was perhaps improved. There was never any secretion.

He first noticed pubic hair at 14 and began to have nocturnal emissions the same year. Intercourse was always satisfactory. The voice remained high-pitched until he took thyroid at 26 at which time the voice became deeper; he could still voluntarily pitch his voice high, and was occasionally mistaken for a girl over the telephone. He started to shave at 21, and now shaves every day. Recession of the hair above the temples was first noticed at 21 and has slowly progressed (see fig. 1, D).

For 5 years he has had mild narcolepsy characterized by uncontrollable attacks of sleeping and cataplexy. Four years ago, he had left renal colic when a small stone lodged at the uretero-vesical junction. He was admitted to the hospital and finally passed the stone. On analysis it contained phosphates and oxalates. He had always been a heavy milk drinker. Serum calcium was 11.5 mg. per cent; serum phosphorus was 3.2 mg. per cent. During the next 4 years, he had a few mild attacks of colicky pain on the left side, during which he passed small stones.

Examination showed a tall, well developed swarthy male. The span was not significantly greater than the height. Axillary, pubic and perianal hair were normal; beard and body hair were heavy. There was marked recession of the hair above the temples. The voice was somewhat high-pitched but definitely masculine and the larynx was normal in size. The breasts were greatly enlarged; the nipples were enlarged and pigmented. The left breast was slightly tender, without masses, and the left nipple was retracted somewhat. No secretion could be expressed. The phallus, scrotum, and prostate were well developed. The testes were quite small, measuring about 2.0 cm. in length. They were firm, normally sensitive and about equal in size. The epididymes were well developed.

Hinton test was negative. Roentgenograms showed a normal sella turcica, normal bone age, and normal kidney outlines without evidence of stones. Intravenous pyelogram showed normal urinary passages. B.M.R. was −12. The urine was of high specific gravity (1.028) and contained large amounts of calcium, many oxalate crystals, a few leukocytes, but no albumin. Cultures showed a light growth of *staph. albus*. Serum calcium was 10.3 mg. per cent; serum phosphorus was 2.8 mg. per cent. Semen examination showed azoöspermia. Biopsy of both testes showed complete hyalinization of the seminiferous tubules and normal appearing interstitial cells (fig. 4, A). Biopsy of the left epididymis revealed entirely normal tissue.

Bilateral subcutaneous mastectomy was performed in July, 1942; the breast tissue showed ductal hyperplasia and proliferation of the periductal connective tissue (fig. 6, B).

Case 7, S.C. (private patient of Dr. H. I. Suby), a 32-year-old married Jewish school teacher, complained of sterility. He had been married for 4.5 years. He had mumps at 10, without orchitis, and had never had any trauma to the testes. At 27 he had a urethral discharge which cleared promptly with methenamine treatment; there were no complications with this infection and no recurrences. He was always obese. Puberty began at 13 and progressed normally; intercourse was satisfactory, and he had ejaculations. Hair and beard growth were normal. At 16 he first noticed prominence of the breasts, which have increased in size very little since that time.

Examination showed an obese, well developed male with normal axillary, pubic and facial hair. The span was not significantly greater than the height. The voice was low-pitched. The breasts were moderately enlarged, not tender, and no secretion was expressed. The phallus,

scrotum, and prostate were fairly well developed and within normal limits. The testes were small.

Semen examinations repeatedly showed azoöspermia. Biopsies of the right testicle showed impaired spermatogenesis with hyalinization of the seminiferous tubules and normal appearing interstitial cells. The patient was treated with chorionic gonadotropin, 750 to 1,000 U intramuscularly 3 times weekly for 3 months without any change in the size of the testis or breasts and without improvement in the appearance of the testis biopsy (fig. 4, B). He continued to have azoöspermia. He was then treated with testosterone propionate, 25 mg. intramuscularly 3 times weekly with no noticeable effect.

Case 8 (fig. 1, E), *C.G.* (*M.G.H. 12047*), a 35-year-old married Jewish porter, was admitted at the age of 31 complaining of sterility and gynecomastia. His general health was always good. He had mumps at 8 without orchitis; he had never suffered any injury to the testes and said they were 'always small.' At 19 an appendectomy was performed; it was noted then that the testes were small and the breasts were enlarged. Puberty began at 14 and progressed normally. At 16 he noticed enlargement of the breasts which progressed for about 3 years and has since remained stationary (fig. 3, B); the breasts were never painful or tender and no secretion was present. He married at 25 and had satisfactory intercourse with ejaculations but no pregnancies resulted. He had slowly gained weight during the last 10 years.

Examination showed an obese, well developed man with smooth skin. There were telangiectases of the cheeks. Axillary, pubic and perianal hair were normal; head hair was heavy and there was a slight recession of the hair above the temples. There was a myopia and a few lenticular opacities; the visual fields were normal. The voice was deep and the larynx was of normal size. The breasts were greatly enlarged and resembled those of an adolescent female; they were not tender and no secretion was expressed. The phallus, scrotum, and prostate were well developed. Both testes were very small.

The FSH was positive for at least 10 M.U. per 100 cc. of urine. Estrin assay was negative for 10 R.U. per liter of urine. The glucose tolerance test was not remarkable. Roentgenograms showed a normal sella turcica, a normal right adrenal after perirenal air injection, and union of the epiphyses of the radius and ulna. Basal metabolic determinations were −20 and −26. Serum cholesterol was 138 mg. per cent. Semen examination showed azoöspermia. Biopsy of the left testis showed almost complete hyalinization of the seminiferous tubules and normal interstitial cells. Biopsy of the right breast showed hyperplasia of the ductal epithelium and proliferation of the periductal connective tissue.

The patient was seen in 1942 with the same complaints. He married again at 32 and his second wife had not become pregnant. The breasts were not changed. During the last year, libido had decreased but he still had erections, intercourse and ejaculations. He shaved only once a week and the beard was limited to the chin and upper lip. It is interesting that his father who had 11 children had the same type of beard.

Examination revealed essentially the same findings as before. The span was not significantly greater than the height. The epididymes as well as the phallus, scrotum and prostate were well developed. The testes were very small, about 1.5 cm. in length, and equal in size. Hinton test was negative.

Case 9 (fig. 1, F), *A.C.* (*M.G.H. 249898*), a 38-year-old married Jewish merchant, was admitted in May, 1940, complaining of sterility. He had married 3.5 years before and his wife had not conceived although no contraceptives were used. After pneumonia at the age of 6 he had infrequent hemoptyses.

Examination revealed bilateral gynecomastia, very small testes and signs of cavitation in the right upper lobe. Roentgenograms showed chronic cystic disease of the right lung; the sella turcica was normal. The visual fields were normal. Semen examination revealed azoöspermia.

In 1942 he was seen again, still complaining of sterility. There was no history of mumps or orchitis. The testes were 'always small.' Puberty began at 12 and progressed normally. He had satisfactory intercourse with ejaculations. He shaved twice a week. Breast enlargement was first noted at 18 when he was thin. During the next few years he slowly gained weight and the breasts increased in size. The breasts were never painful or tender and had not changed in size for the last 10 years (fig. 3, C).

Examination showed a well developed muscular man. The span was 4.5 cm. greater than the height. Axillary, pubic and perianal hair were abundant; head hair was heavy and there was recession of the hair line above the temples. The beard was limited to the chin and upper lip, but was quite heavy. The voice was deep and the larynx normal in size. The breasts were greatly enlarged, but not tender and no secretion was expressed. There were signs of cavitation over the right upper lobe. The phallus, scrotum, and prostate were normal. The testes were extremely small, equal in size and firm. Hinton test was negative. The patient refused to have a testicular biopsy performed.

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Clinical Evaluation of Estrone, Estradiol Benzoate and Diethylstilbestrol

[Menopause]

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DURING the past several years a large number of articles have been published concerning the scientific and, oft times, speculative aspects of therapy with various estrogenic hormones. Physicians concerned with practical clinical results, and cost per treatment, will find few data in the literature on the relative effectiveness, duration of action, tolerability and cost of the various types of estrogenic substances. However, the physician in his daily practice is interested in how he can attain the best results with the least possible risk of side-effects, and at a cost within the means of his patient. With this in mind, we instituted a survey of a group of more than 200 patients over a considerable period of time.

MATERIAL AND PROCEDURE

The series under investigation consisted of women in the menopause. The group of patients represented many races, colors and nationalities. In our clinics at Metropolitan and Flower-Fifth Avenue hospitals the patients treated were from among the poorer classes. They included Porto Ricans of Spanish and mixed descent, Italians, Negroes, Jews and a smattering of other nationalities and races. The patients in our private practice, located in a suburb of New York City, were white and financially were of the better class. Thus it will be seen that a fair cross section of New York's polyglot population was surveyed and peculiarities incident to certain groups were eliminated.

The cases ranged from mild menopausal types to those with more severe symptoms of the surgical menopause. However, the majority of cases represented patients with similar symptoms and of not too severe a nature. The patients were divided into 4 groups of 50 each. Those in *group 1* received preparations of estrone,[1] which is a product of partial metabolic inactivation of estradiol; those in *group 2*, received α-estradiol benzoate,[2] the synthetically derived benzoic ester of the primary follicular hormone; *group 3* received diethylstilbestrol,[3] the new synthetic estrogen which, in contra-distinction to the other two compounds, does not occur naturally in the body; *group 4* were treated with ovarian extracts, sedatives and a male hormone preparation.

At the initiation of the investigation, therapeutic effects were measured by estimations of urinary estrin and examination of endometrial biopsies and vaginal smears. Later these procedures were discontinued because of difficulties encountered in correlating some laboratory findings with the subjective response experienced by patients. Therefore, clinical results became the sole criterion for evaluation.

The commonly used parenteral dosage for estrone and estradiol benzoate is 10,000 I.U. (1 mg.) of the former and 2000 R.U. (0.33 mg.) of the latter. These are the arbitrary dosage levels employed in most instances in the respective groups.

Most of the patients in *groups 1* and *2* were checked as a 'control' and by giving injections of sterile water it was possible to determine whether psychic factors were responsible for the improvement experienced by the individual. Within 4 to 14 days after initiation of the sterile water injections, all of the women complained of the original ailments. Resumption of hormone treatment brought about such remarkable improvement that there can be no doubt as to the efficacy of the therapy.

Diethylstilbestrol, when injected, was given to most of the patients in doses of 1 mg. Many of those in *group 3*, receiving diethylstilbestrol, as well as some represented in *groups 1* and *2*, were given diethylstilbestrol orally in daily doses of 1.0, 0.5 and 0.1 mg., respectively. The total number of patients

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[1] The estrone employed was supplied by E. R. Squibb and Son, New Brunswick, N. J. (Amniotin); Parke, Davis & Co., Detroit, Mich., (Theelin); and Endo Products, New York City (Estromone).

[2] The α-estradiol benzoate (Dimenformon Benzoate), was supplied by Roche-Organon, Inc., Nutley, N. J.

[3] The diethylstilbestrol (Metestrol) was supplied by Metropolitan Laboratories, New York City.

thus changed to oral therapy with diethylstilbestrol approximated the number present in each original group. Also, as the study progressed, in some of the cases receiving estrone, therapy was changed to estradiol benzoate and vice versa; likewise, patients received diethylstilbestrol injections, supplemented with diethylstilbestrol orally, after their response to estradiol benzoate or to estrone had been evaluated. The reverse sequence was employed in other instances, in which patients were first treated with diethylstilbestrol, orally or parenterally, and therapy was changed to either estrone or estradiol benzoate. Many patients were rotated to all the groups, eventually being returned to estradiol benzoate therapy.

Dosages and side-effects. There were 2 women in each of the three original groups of patients treated with estrogens, who developed sore buttocks characterized by a rash and swelling at the site of injection. When therapy was changed so that each of these patients received a different estrogenic substance, similar reactions recurred. When given placebos of oil, these patients likewise showed identical by-effects indicating the allergy was toward the oil and not the estrogens.

In the group receiving estrone, it was found that, in the average case, the dose of 10,000 I.U. was sufficient to control the menopausal symptoms for from 4 to 6 days. There were a few instances in which relief could be obtained only when two injections per week were given, and a smaller number in which partial relief only was obtained even though injections were given as frequently as three times a week.

The group of patients receiving α-estradiol benzoate experienced the most prolonged beneficial effects. Most of the patients, on a dose of 2000 R.U., were kept symptom-free for 8 to 10 days, although a few required more frequent injections while a number were able to go as long as 2 to 3 weeks between injections. Aside from the local reactions previously noted, which definitely were not attributable to the therapy, no untoward side-effects were observed in the groups receiving the estrone or α-estradiol benzoate.

Group 3, receiving diethylstilbestrol, is of special interest because of the comparatively recent introduction of the medication. It was found that if injections of 1 mg. were given, the interval between injections and recurrence of symptoms was very short. By increasing the dose to 2, and even 5 mg., the period between injection and recurrence of symptoms was not markedly increased, but the toxic phenomena were manifested more promptly, and were more severe. By-effects included nausea and vomiting, skin rash and soreness or fullness of the breasts. Two patients complained of insomnia and disturbing dreams when they did fall asleep. The symptoms disappeared when the dosage was reduced or after rest periods of about a week.

Diethylstilbestrol is the only estrogen therapy used in the study where an oral administration to a large number of patients was attempted, and here the greatest percentage of toxic manifestations was observed. With a daily dose of 1 mg., there was nausea and vomiting in 4 cases, 8 per cent. Nausea alone was noted in 7 additional cases, or a total with gastrointestinal phenomena of 22 per cent. When the dosage was cut to 0.5 mg. daily, the incidence of gastrointestinal symptoms decreased to 6 per cent, and on a dosage of 0.1 mg. twice daily, only one patient, or 2 per cent of the series, reported nausea. Unfortunately, when the dosage was so decreased, the effectiveness was so lowered that it became a question whether the side-effects of the diethylstilbestrol were less objectionable than were the occasional hot flushes, vertigo and similar menopausal manifestations.

The results observed with ovarian extracts are definitely inferior to those attending the use of either estradiol benzoate or estrone. In some instances sedatives gave relief from such symptoms as emotional instability or excitability; other manifestations, however, such as flushes or vertigo did not abate on sedation alone. Testosterone propionate proved definitely beneficial, but its use was, in our hands, limited to cases with a tendency to uterine hemorrhages.

CASE REPORTS

The following case histories illustrate the procedure employed to evaluate the various substances and also the results attending therapy.

Case 1. *S.D.*, white, age 43, para 2. Except for influenza in 1918 and cystitis in 1939, there had been no serious illnesses and no operations. The menstrual history was a normal one. When she was first seen in October 1940, the patient complained of pain in the precordial region, vertigo and hot flushes. Physical examination, including an electrocardiogram, revealed no cardiac pathology. The Wassermann reaction was negative. Therapy with estrone, 10,000 I.U. parenterally, twice a week for 6 injections was followed by marked symptomatic improvement. Injections of the hormone were then replaced by injection of sterile water without the patient's knowledge; after 2 weeks the symptoms became as severe as at the beginning of treatment or more so. Therapy with 2000 R.U. of estradiol benzoate parenterally, once a week, was instituted in January, 1941. Complete symptomatic relief followed the 4th injection. A vaginal smear, made on February 4, showed little cornification, round or oval atrophy cells being prevalent, notwithstanding subsidence of clinical symptoms. In March, therapy was shifted to diethylstilbestrol orally, 0.5 mg., twice a day. There was slight nausea and pruritus of the thorax and genital region. The pruritus subsided after about 6 days. Subsequent recurrence of daily hot flushes and vertigo under this regimen necessitated a return to therapy with es-

tradiol benzoate parenterally. Under the latter the patient again became symptom-free, remaining so to date (June, 1942) on a maintenance dose of 2000 R.U. every other week.

Case 2. M.M., a white female of Spanish descent was 31 years old. There had been a unilateral oöphorectomy performed in August, 1935. Following this the intervals between menses, which preoperatively had occurred regularly every 28 to 31 days, increased to 2 to 3 months. When first seen, Feb. 1, 1940, the patient complained of amenorrhea (last period October, 1939), severe attacks of hot flushes, vertigo, nervousness and pain in the precordial region. The face and upper extremities showed a wide-spread acne vulgaris which occurred after cessation of menstruation. An electrocardiogram was negative, although the chest plate showed slight enlargement of left ventricle and slight accentuation of the arcs of the pulmonary artery and left auricle. Therapy with estrone, 10,000 I.U. parenterally, twice a week was instituted. On Feb. 29, 1940, the patient reported improvement. Bleeding occurred on March 2 and 23 at which time she was symptom-free. A reduction of the dosage to one injection of 10,000 I.U. of estrone weekly was followed by return of symptoms, June 18. From then on 2000 R.U. of estradiol benzoate was given once a week instead of the estrone. This dose sufficed to relieve completely all symptoms. Medication was continued until Sept. 10, 1940, the patient experiencing a sense of well-being at all times. Injections of hormone were then replaced by injections of sterile water and 1 mg. of diethylstilbestrol per day orally was given simultaneously. By November, 1940, severe headache, hot flushes, marked vertigo, fatigue and sluggishness were manifested. On November 1, injection of 1 mg. of diethylstilbestrol, twice a week, was substituted for the oral therapy. The flushes and vertigo were relieved to some extent, but the symptoms did not clear up completely. In February, 1941, therapy was changed again to estradiol benzoate, parenterally, 2000 R.U., once a week. Complete symptomatic relief followed the fifth dose. The patient remained symptom-free except for an occasional slight flush on a maintenance dosage of 2000 R.U. every other week, which dosage was instituted on March 15, 1941. Headache, present when diethylstilbestrol was administered, did not recur after discontinuance of therapy with the substance or when other estrogens were given.

Case 3. A.A., age 37, gravida 1, nullipara. Menarche occurred at 15 years of age, with menstrual cycles 25 days in length, menstruation lasting 3 to 4 days. When the patient was first seen in February, 1940, she complained of irregularity in the menses for the previous 6 months. The bleeding periods recurred at intervals of 50 to 65 days with a scanty flow. Hot flushes, vertigo, and extreme nervousness were also experienced. The symptoms cleared up promptly with estradiol benzoate, 2000 R.U. parenterally once a week. Menses became more frequent but there was no change in the amount or duration of flow. In April, injections were discontinued and diethylstilbestrol, 1 mg. orally were given daily. The occurrence of severe nausea and vomiting prompted reduction of the dosage to 0.5 mg. of diethylstilbestrol daily. On this smaller dose there was recurrence of flushes and complete anorexia. In May, 1940, oral medication with diethylstilbestrol was discontinued, being replaced with estradiol benzoate parenterally, 2000 R.U., once a week. On July 9, 1940, the patient was symptom-free and was discharged. Observations at intervals of 3 months showed no recurrences of symptoms (March, 1942).

Case 4. S.L., age 57, nullipara. Menarche at 13 with cycles of 28 to 30 days and a menstrual flow lasting 5 to 6 days with occasional slight pain. Menses ceased at the age of 53 and the patient had infrequent hot flushes and spells of vertigo for which she did not seek medical attention. In September, 1938, she presented herself for examination because of spotting every few days for the previous 6 weeks. Upon manual examination a small nodule on the anterior aspect of the uterus was found. Curettage revealed the presence of carcinoma and a panhysterectomy was performed immediately following the diagnosis. The pathologist's report indicated a carcinoma adenomatosum. The convalescence following operation was uneventful. The patient returned in January, 1939, complaining of a typical anginal syndrome. An electrocardiogram revealed an inversion of the T-wave and depression of the S-T segment. Associated with this change were frequent hot flushes, vertigo, nervousness and insomnia. Physical examination revealed an apex rate of 96 per minute with a well-defined diastolic murmur at the apex. There were no evidences of carcinoma at the site of operation or in any other part of the body. Estradiol benzoate parenterally, 2000 R.U., twice a week, for 5 doses, was followed by complete relief of symptoms. After the 12th injection a second electrocardiogram revealed a normal pattern. The patient has been seen once a month up until June, 1942, and several electrocardiograms made subsequently have been negative. With improvement in cardiac symptoms, the hot flushes and other menopausal symptoms have disappeared as well.

Case 5. N.V., age 38, para 3, gravida 3. Menarche occurred at 12, with cycles 28 to 30 days in length, and menstrual flow for 4 to 6 days, pain preceding the onset and lasting for first day. Following childbirth, the patient experienced occasional dysmenorrhea. In July, 1940, a pan-hysterectomy had been performed because of uterine fibroids and cystic ovaries. When the patient was first seen in October, 1940, she complained of severe dizzy spells, headache (both frontal and occipital) and hot flushes. Diethylstilbestrol, parenterally, 1 mg. was given twice a week. A vaginal smear, made after 6 weeks under this regimen, showed epithelial cornification but there was no abatement of symptoms. Injections were supplemented by 1 mg. of diethylstilbestrol, orally, per day. This resulted in only slight improvement. After 12 weeks of treatment with diethylstilbestrol, therapy was changed to estradiol benzoate, 2000 R.U. parenterally, twice a week. The clinical response was prompt and the patient became symptom-free after 3 weeks. Subsequently, the dosage was reduced to 2000 R.U. of estradiol benzoate once a week, on which dosage the patient remained symptom-free for more than 3 months. In May, 1941, therapy with estradiol benzoate was discontinued and diethylstilbestrol, 1 mg. orally was administered once daily. After 2

weeks, the symptoms returned and the patient requested to be given the parenteral treatment. Estradiol benzoate, 2000 R.U., every other week was given and continued until December, 1941, when the patient was discharged. Re-examination in February and May, 1942, showed the patient to be comfortable and without symptoms except for an occasional slight hot flush.

Cost of Treatment

The following table illustrates the efficiency of the three estrogens, estrone, estradiol benzoate, and diethylstilbestrol, in comparison with the cost of treatment.

Drug Used	Average Duration of Effect	Toxic Reaction	Average Cost to Patient per Unit of Treatment[1]	Average Adjusted Monthy Cost
	days			
Estrone, 10,000 I.U. = 1 mg. (parenterally)	4–6		$1.10	$6.60
α-Estradiol benzoate, 2000 R.U. = 0.33 mg. (parenterally)	8–10		$0.65	$2.16
Diethylstilbestrol; 1 mg. (parenterally)	2–3		$0.16	$2.00
Diethylstilbestrol tablets; 1 mg. (orally)	1	22%	$0.0135	$0.41

[1] Prices based on those charged in representative drug stores in midtown and suburban New York. Figures for diethylstilbestrol are based on average prices charged for a low-priced brand.

DISCUSSION

From the foregoing data, it is obvious that diethylstilbestrol has the benefit of being low in cost. However, the reactions and toxic by-effects observed in this study call for caution and a careful test to determine individual sensitivity to the drug before prescribing it.

Most interesting is the observation that those patients originally treated with estradiol benzoate, if treatment was changed to estrone, had to be given more frequent injections than those who were treated initially with estrone. Those whose treatment started with estradiol benzoate had experienced the sense of well being that may be attained with comparatively small doses of this compound. Subsequently, more frequent injections, or, in terms of units per month, higher doses of estrone were required to alleviate symptoms adequately than was the case with those patients who originally were treated with estrone and who had never experienced the maximum sense of well being attending the use of estradiol benzoate. Conversely, if therapy of patients with estrone were changed to estradiol benzoate, not only were less frequent injections necessary, but the patients also experienced a greater sense of well being.

Furthermore, it was observed that patients who initially received estradiol benzoate, particularly cases of surgical menopause, when therapy was changed to diethylstilbestrol, required both parenteral and oral doses of the latter compound to maintain comfort. In the present series, diethylstilbestrol was effective in the doses administered in only 30 per cent of the cases, in which the patients initially had received estradiol benzoate.

In a recent report, Stoddard and Metzger (1) discussed comparative effectiveness and costs of estrogenic therapy and reached conclusions which differ somewhat from our own. These differences, it would seem, are the result of using different methods of evaluation. Stoddard and Metzger employed the technic commonly used in determining estrogenic effects in animal experimentation, whereas we observed that complete cornification of the vaginal cells may occur without relationship to relief of symptoms, and hence vaginal smears may not always be a reliable index to therapeutic response. For this reason we discontinued making vaginal smears shortly after the study was instituted, and thereafter relied solely on clinical response as an index to potencies, dosages and cost of treatment.

It is also observed that Stoddard and Metzger base their findings on studies of women of the postmenopausal period (55 to 70 years of age) who, without exception, were mental patients. In our series, aside from a few pre-menopausal cases, patients were at the beginning of the menopause, natural as well as surgical, and none was a mental case. It is also to be noted that evidently endocrine balance had been already fully established in the group studied by Stoddard and Metzger, which was the reverse of our series. This difference in the type of patient, particularly as regards mental status and age, naturally has a bearing on the observations and is perhaps the basis on which vaginal smears were chosen by Stoddard and Metzger as the method of measuring response.

The fact that the cases in the group studied by Stoddard and Metzger represented patients who apparently were not in the distress because of climacteric symptoms and whose mental status made their testimony unreliable, no doubt accounts for the 10-day period of observation as defined by the authors. In our series, all of the patients presented symptoms requiring treatment over an extended period of time. Results were judged solely by the degree of comfort

experienced by the patient during the period of endocrine adjustment. We are inclined to believe that caution should be exercised in comparing the results observed by Stoddard and Metzger with those reported herein. In the one study, the methods of bioassay commonly employed in animal experimentation served as an index of therapeutic effectiveness, whereas in the other, (our own) clinical methods alone were used. As an instance, in the clinic one observes the slow absorption of estradiol benzoate which makes spacing of doses possible, while such a response in an animal under observation for a week or 10 days and receiving daily injections cannot be accurately measured.

SUMMARY AND CONCLUSIONS

A series of more than 200 menopausal women, in four groups of equal size, was subjected to treatment with estrone, parenterally, estradiol benzoate, parenterally and with diethylstilbestrol, some of which was given orally, some parenterally; the fourth group received ovarian extracts, sedatives and a male hormone preparation. By rotating patients to various groups of treatment it was attempted to evaluate therapeutic potencies and the cost of treatment.

Side-effects such as gastro-intestinal phenomena were observed in 22 per cent of the group receiving diethylstilbestrol. While the cost of this estrogen, not native to the body, is low, the toxic reactions it elicits call for caution in its use. Estrone and estradiol benzoate were well tolerated. When symptoms require more constant supervision, and by-effects are to be avoided, or if there is lack of co-operation on the part of the patient, parenteral is preferable to oral therapy. Results observed in the present study lead to the conclusion that the α-estradiol benzoate is the estrogen of choice. Injections can be spaced conveniently because of the protracted action of the esterified compound and its cost is far lower than that of estrone.

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Oral Hormone Therapy in Anovulatory Bleeding

[Ovarian Failure]

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COMBINED EFFORTS in various fields of investigation have contributed to the understanding of the physiologic background of menstruation. In a slow but steadily progressive course, theories of the earliest writers have yielded to more concrete knowledge as developed from the application of anatomic, physiologic and biochemical facts. These facts were augmented by biologic experimentation built around the physiology of the female generative apparatus and centered in the theory of the dominating rôle of the corpus luteum in the mechanism of menstruation

Contradictory to this construction, is the observation of the non-ovulatory menstruation. The work of Corner (1) and Hartman (2) proved that anovulatory bleeding occurs in the Macacus rhesus occasionally and at times other than during the summer months. Novak (3) in 1930 transferred these facts to the realm of human physiology, assuming that certain types of irregular bleeding, although of a cyclic character, likewise occur without the activity of the corpus luteum.

The following case, observed in the Endocrine Clinic of the Woman's Hospital, was studied over a comparatively long period. It is presented as a contribution to the problem of aluteal bleeding and as evidence that such a condition can be influenced by therapeutic methods.

CASE REPORT

Mrs. M.C., 32 years old, was seen first Sept. 7, 1940. Complaints: For the last 2 years, severe pounding headaches at frequent, irregular intervals, increasing before menstruation; fatigue and the feeling of fullness. The menstrual cycle, which was regular up to two years before admission, is now of a 35 to 45-day type and the flow is gradually decreasing in amount.

The patient is of feminine configuration, moderately obese, 5 ft. 3 in. tall, and weighs 172 lb.; she has lost 20 lb. during the last 3 years. The B.M.R. was minus 8%. Pelvic examination revealed a somewhat enlarged uterus in normal position and normal adnexa.

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On Sept. 21, 1940 an endometrial biopsy (premenstrual phase expected) showed a proliferative phase of the endometrium with numerical decrease of glands. A diagnosis of edema of proliferative endometrium was made (fig. 1). The patient was given diethylstilbesterol, 1 mg. daily, which was tolerated without side effects. On Oct. 5, 1940 bleeding occurred, lasting 5 days. This was considered by the patient, to be the first normal menstruation in several years.

An endometrial biopsy on Nov. 2, 1940 was diagnosed as hyperproliferation of endometrium of mild degree (fig. 2). Bleeding occurred Nov. 3 to 8, 1940. This was considered by the patient to be identical with normal menstruation; since in the preceding curettage, November 2, a luteal phase could not be detected, this bleeding was considered to be of the aluteal type.

Treatment with diethylstilbestrol was discontinued and she was given pregneninolone, 60 mg. daily for 7 days preceding the next expected period. Bleeding occurred on Dec. 1, 1940 the character of which had not been determined by an endometrial biopsy prior to onset of flow. During the second half of the following cycle, 80 mg. of pregneninolone was given daily for 2 weeks. An endometrial biopsy made Dec. 28, 1940, was diagnosed as a non-secretory endometrium in a moderately hyperproliferative state; the hypertrophic process was less pronounced than in the previous curettage (fig. 3). Bleeding for 7 days of moderate extent began on Jan. 1, 1941.

On Feb. 3, 1941 the patient was given pregneninolone, 60 mg. daily for 5 days, followed by 100 mg. daily for 7 days, a total of 1000 mg. being given. An endometrial biopsy made on Feb. 15, 1941 was diagnosed as a fully developed secretory phase (fig. 4). Menstruation began on Feb. 17 and continued until Feb. 22, 1941.

During the second half of the following cycle, the patient was given 1000 mg. of pregneninolone. On the first day of menstruation March 15, 1941, an endometrial biopsy again revealed a full secretory phase (fig. 5).

During the next period the patient received no therapy. An endometrial biopsy made on April 11, 1941 was diagnosed as a well-built premenstrual endometrium; two days prior to onset of menses after a four weeks' pause in medication (fig. 6).

Subsequently the patient was given small doses of desiccated thyroid extract, no other hormone therapy being given. In April, May, August, and October of 1941 endometrial biopsies were made close to the expected

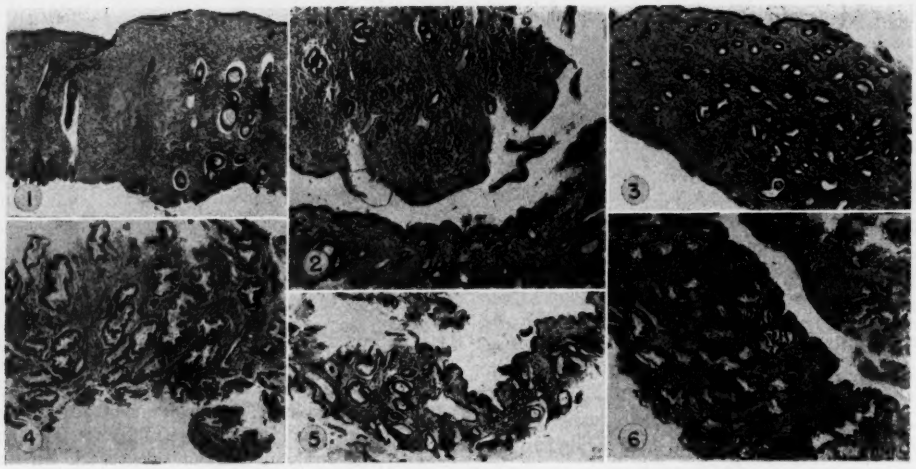

Fig. 1. Biopsy obtained Sept. 21 1940. Proliferative endometrium.

Fig. 2. Biopsy obtained Nov. 2, 1940 following therapy with 1 mg. of diethylstilbestrol daily since Sept. 21, 1940. Previous menstruation Oct. 5–9. Hyperproliferation of mild degree. Menstruation followed on Nov. 3 and lasted 6 days.

Fig. 3. Biopsy obtained Dec. 28, 1940 after 2 weeks of treatment with 80 mg. of pregneninolone daily. Non-secretory endometrium, moderate proliferation. Menstruation followed on Jan. 1 and lasted 7 days.

Fig. 4. Biopsy obtained on February 15, 1941 after receiving a total of 1000 mg. of pregneninolone in the 12 days preceding the biopsy. Secretory endometrium. Menstruation followed on Feb. 17 and lasted until Feb. 22, 1941.

Fig. 5. Biopsy obtained Mar. 15, 1941 on first day of menstruation. Patient had received 1000 mg. of pregneninolone during second half of cycle. Secretory endometrium.

Fig. 6. Biopsy obtained Apr. 11, 1941, two days before onset of menses. No treatment had been given during this cycle. Secretory endometrium.

onset of menstruation; all revealed a secretory endometrium, normal for the premenstrual phase. Menstruation occurred at regular intervals of 28 days and were of normal character. Coinciding with the return of the normal type of uterine bleeding, the physical condition of the patient improved and she reported she was well when last seen.

In analyzing this case it may be emphasized that experimental investigations seem to indicate that menstruation is essentially composed of two phenomena, *a*), the dissolution of the structure of the endometrium initiated by a sharp drop in the level of the ovarian hormones, which is coinciding with a liberation of the pituitary hormone; *b*) the bleeding mechanism proper. The postulate that the corpus luteum is the dominating factor responsible for menstruation, as it follows from the work of Fraenkel (4), was irreconcilable with newer viewpoints evolved from the recognition of the anovulatory cyclic bleeding in the monkey and in the human female from a non-secretory mucosa. This fact *per se* lends support to the concept that the bleeding mechanism is independent of the corpus luteum and is in all probability essentially a vascular phenomenon. The corpus luteum, therefore, is the responsible factor for the transformation of the proliferative endometrium into a secretory mucosa and for the maintenance of secretion. The fact that cyclic uterine bleeding, menstrual or intermenstrual, is preceded by a sudden drop in the level of the female sex hormone, lends support to the assumption that the female sex hormone plays an essential rôle in cyclic uterine bleeding.

Experimental neurology has brought to light the importance of the hypothalamus as the center of a neuro-glandular mechanism, which also controls, among other vegetative functions, some activities of the generative apparatus (5). Hohlweg and Junkmann (6) have shown by their experiments that the sex hormones do not act directly upon the hypophysis by way of the blood stream, and conclude that an interpolated sex center, presumably represented by the hypothalamus, acts as a regulator between these two organs. The vascular phenomenon in menstruation, therefore, may result from the vasomotor stimulation of the uterus (endometrium) generated by the neuro-glandular interaction and, therefore, is temporally linked with the gonad activity. Subsequently the cyclic uterine bleeding may be maintained by the sex center also under conditions in which the hormone constellation necessary for normal menstruation is disturbed, such as in anovulatory menstruation, when the corpus luteum hormone is not produced.

With reference to the effectiveness of the substitutional hormone supply in the case presented, one may be well justified in assuming restoration of the entire physiological mechanism of the menstrual cycle

by supporting all tissues involved in their intrinsic readiness to respond. By administration of those hormones produced in the sequence of a complex physiological process, such as menstruation, one may promote recuperation and thereby readjustment of normal function, which when unaided, may be greatly delayed or not resumed at all.

The first three endometrial biopsies, which preceded the first three bleeding episodes under observation, combined with the physical symptoms, may give suggestive evidence that the patient was in a state of disturbed hormonal balance. Restoration of normal function became manifest only after the hormone supply was increased to the required optimum, which was affected by oral administration.

The pregneninolone (Progestoral) was supplied by Roche-Organon Inc., Nutley, N. J., by the courtesy of Dr. Leo A. Pirk.

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Treatment of Acne with Orally Administered Estrogens[1]

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IN A PREVIOUS paper (1) we proposed the thesis that acne is caused by a disturbance of the normal balance between androgens and estrogens. When the imbalance becomes such that there is a preponderance of the androgens the acnegenic action of the androgens which Hamilton (2) has demonstrated, is exerted.

Iu support of this thesis we reported (1) the results of assays of androgens and estrogens in 33 female patients with acne. The results of the assays indicated significant androgen preponderance as compared to normal standards. No assay of urine from males was reported, for we were unable to obtain dependable estrone equivalent values from males.

If this thesis concerning the cause of acne is correct, it should be possible to bring about the disappearance of the eruption by administering sufficient estrogen to restore the androgen-estrogen balance to normal, and males as well as females should respond to the treatment. The present communication concerns the results of such treatment in 25 individuals, 14 females and 11 males.

SUBJECTS

The histories and physical findings in the group yield certain data which demand brief discussion. The well-known association of acne with adolescence, and its tendency to spontaneous remission toward the end of that period, make the age factor extremely important in interpreting our results. In this series only 3 females and 4 males were under 20 years of age. The average age of the 14 women was 25.8 years, that of the 11 males, 20 years. It seems unlikely therefore, that spontaneous remission can be an important source of error in evaluating therapy in this series.

The duration and severity of the process must also be considered in interpreting results, since the tendency to spontaneous remission of mild and recent eruptions is common. In 5 of the patients the duration of the acne was between 1 and 5 years; in 12, between 5 and 12 years; in 4, between 12 and 20 years; and in the remaining 3, between 20 and 30 years. The average duration for the group was 9.1 years. The process was graded as *a*), moderately severe, 12 patients; *b*), severe, 10 patients; and *c*), extremely severe, 3 patients. No patient was included in the series who had had, during the preceding year, any marked improvement in the condition. Nineteen had had previous treatment with roentgen-ray, ultraviolet light, or 'sun lamps,' without benefit. Possible error due to spontaneous remission would, therefore, be minimal.

In the group of 14 female patients there was none whose menstrual history was normal. Seven complained of severe dysmenorrhea, 8 of hypomenorrhea, and 2 of menorrhagia. In 13 there were definite exacerbations of the acne at the time of menstruation, followed by variable improvement, never amounting to complete disappearance, during the intermenstrual intervals.

TREATMENT

The patients were treated either with diethyl stilbestrol or with ethinyl estradiol[2] by mouth. Twenty received diethyl stilbestrol; five, ethinyl estradiol. The initial dose of the former was 0.5 mg. daily until tolerance was determined. In 17 patients it was then increased to 1 mg. daily, and in two mature males with severe chronic acne to 1.5 mg. and 2.0 mg. daily. In women the medication was omitted 4 days before the predicted menstrual period, and resumed 48 hours after menstruation had ceased. Therapy was uninterrupted in males. In only one patient was it necessary to stop the diethyl stilbestrol because of persistent digestive disturbance. When ethinyl estradiol, 0.15 mg. daily, was used there was no disturbance. None of the males experienced any digestive disturbance. In two males slight gynecomastia, and in one,

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[2] The ethinyl estradiol was supplied by the Schering Corp., Bloomfield, N. J., through the courtesy of Dr. Erwin Schwenk and Dr. Max Gilbert.

pigmentation of the nipples, appeared, but receded rapidly when treatment was omitted in the two who have remained under observation. This reaction suggests that it may be wise to employ intermittent treatment in males as well as in females.

Ethinyl estradiol was administered in initial doses of 0.15 mg. daily. This was later increased to 0.3 mg., if the response was unsatisfactory. No unpleasant reactions were observed, and it appeared to be as effective as stilbestrol.

RESULTS

Fifteen of 25 patients (60% of the series) became entirely free from acne after periods of treatment varying from 2 to 6 months. Two patients, whose treatment was intermittent, became free in 8 and 9 months, respectively. The 8 remaining patients are still under treatment, and all show improvement, varying between 50 per cent, in a woman of 36 with acne and hirsutism of 21 years' duration, and 90 per cent, in 4 months, in a boy of 13 with severe generalized acne of the face, neck, chest and back. No patient has completely failed to respond. All of the female patients, with the exception of the one with hirsutism, have shown a synchronous improvement in menstrual difficulties of a degree comparable to the response of the acne.

DISCUSSION

The high incidence of abnormal menstruation in our series cannot be explained on the theory of chance, and furnishes a basis for believing that acne is associated with an imbalance of hormones, the nature of which is suggested by the characteristic cyclic variation in the severity of the eruption. During catamenia, the estrogens are low, while the androgens do not fluctuate significantly (3–6). There is, therefore, a relative estrogen deficiency at the time of exacerbation of the acne at menstruation, and the eruption improves, or even disappears in the mild cases, as the estrogens increase to their mid-cycle peak. Geist and his associates (7) have shown that the injection of testosterone in women brought about 'regressive changes in the endometrium and vaginal smears characteristic of estrogen deficiency,' and that, coincidentally, mild acne appeared in a number of patients, and disappeared as endometrium and vaginal mucosa regenerated rapidly following the cessation of the testosterone injections.

If their conclusions and our deductions are valid, it should be possible to cause the disappearance of acne in an individual by producing, by means of therapy, a constant increase in the estrogens in the body of sufficient magnitude to restore the normal dynamic estrogen-androgen balance.

Our initial experiments with gonadotropic and estrogenic therapy furnished intriguing, but unsatisfactory, results (8, 9). In some adolescents with mild acne, complete and apparently permanent disappearance of the acne followed treatment with urinary gonadotropic extracts, but in the older patients with more severe acne good results were partial and the benefit temporary. These suggestive, but unconvincing, results may have been due to failure of ovarian response to the dosage used, as seems especially likely in the adults, or to the fact that it was impossible in most cases to give the injections as often and as long as necessary. Similar results were obtained with injections of estrogens, all of which suggested that the unsatisfactory response might be due to insufficient or ineffective therapy.

The response to estrogen therapy in the present series of patients furnishes, we believe, evidence concerning the cause of acne. As an isolated study our series is too small to afford conclusive proof, but if the results are correlated with biological and experimental data, they become significant. A brief recapitulation of these data is, therefore, pertinent.

The most significant of these biological facts are: *a*) that acne does not occur spontaneously in male castrates, and is extremely rare in the first decade of life, a time when both androgens and estrogens are present in only minimal amounts (10); *b*) acne is characteristically associated with adolescence, during which time both estrogens and androgens are normally increasing rapidly (in amount); and *c*), acne usually disappears spontaneously in early adult life when the normal dynamic balance between estrogens and androgens has become established. As a corollary, the high incidence of abnormal menstrual cycles in adult female patients with acne indicates that failure to establish such a normal balance, or its interruption (by a masculinizing tumor, for example), is a common factor in both the acne and the abnormal menstrual cycle.

The exact nature of this disturbance cannot be determined from this biological evidence, although the close association of acne and masculinizing tumors, and the high androgen titers, suggests that an excess of 17-ketosteroids is the determining factor in acnegenesis. This suggestion is supported and clarified by Hamilton's observation that injections of testosterone will produce acne in many, but not all, male castrates, (2) and by the observation of Geist and his associates (7) that some, but not all, of their female patients treated with testosterone developed temporary acne during treatment. The only possible interpretation of these results is that the so-called 'male hormone' is acnegenic, but that it can produce acne only in individuals who are not normally resistant to its acnegenic potentialities.

The factors which determine this resistance are, as

emphasized in our previous paper (1) probably multiple, but as was also pointed out, both biological evidence and hormone assays suggest that the controlling factor is a disturbance of the balance between androgens and estrogens, resulting in insufficient estrogenic potency to protect the individual from the acnegenic effect of androgens. The biological evidence consists in the well-known menstrual exacerbation and inter-menstrual remission of acne in certain women. The levels of androgens have been shown to remain fairly constant throughout the menstrual cycle (3, 4), while the estrogens show a cyclic variation, reaching their lowest level at the time of menstruation and their highest level at about the middle of the cycle. The association of the excerbation of acne with catamenia, and the remission during mid-cycle, therefore, furnish further evidence of this anti-acnegenic property.

The results of adequate estrogenic therapy in patients of both sexes, as reported in this paper, furnish, we believe, further evidence that acne is caused by a disturbance of the normal functional balance between androgens and estrogens, and that when the preponderance of the androgens becomes sufficient in an individual, that it exerts a specific acnegenic effect. If this be true, the diagnostic significance of acne, and the method of treating it successfully, are also established.

SUMMARY AND CONCLUSIONS

Twenty-five patients (14 females and 11 males) with acne, were treated with diethyl stilbestrol or ethinyl estradiol. Fifteen patients (60%) became entirely free from acne in from 2 to 6 months. Two more, in whom treatment was intermittent, became free in 8 and 9 months. The 8 remaining patients are still under treatment, and all show improvement. No patient has completely failed to respond. The biological and recent experimental evidence concerning the cause of acne is reviewed and it is concluded that such evidence, together with the results of adequate estrogen therapy, furnish evidence that acne is caused by a disturbance of the normal functional balance between androgens and estrogens when the preponderance of the androgenic factor becomes sufficient to exert its specific acnegenic effect in a given individual.

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Dosage of Female Sex Hormones, Estradiol and Anhydrohydroxyprogesterone by Sublingual Application

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SOME TIME ago I reported in this journal on favorable results which had been obtained by the sublingual administration of methyl testosterone (1). Good results had been observed with the female sex hormone, estradiol, by this form of application, both in animal experiments (2) and clinically (3–6). It has been deemed desirable to determine the dosage of female hormone necessary to produce the proliferative and secretory phase in the human endometrium by sublingual application, particularly in view of the fact that no such reports are today available. It is known that dosages as high as 450 mg. of estradiol administered per os are not sufficient to produce endometrial proliferation in a castrated woman (3); according to Herrenberger this can be done with 180 mg. of estradiol in alcoholic solution by sublingual administration. Giesen (5) succeeded in producing proliferation of the uterine mucosa with dosages of 150 to 180 mg. of estradiol, in the form of tablets which he allowed to dissolve in the mouth. In animal experiments Miescher and Gasche (2) showed that the action of estradiol on the uterus of the castrated female rat is 10 to 20 times more intense sublingually than orally.

On the basis of these observations, 6 women between 48 and 55 years of age who had had roentgen therapy 2 to 3 years previously because of recurring metropathy and who subsequently suffered from severe ovarian deficiency symptoms were chosen for the following experiments. They were given tablets of estradiol and of anhydrohydroxyprogesterone especially prepared for sublingual administration.[1] These hormones are mixed with mucilaginous drugs and emulsifying agents which promote absorption and are then compressed at high pressure. The patients placed the tablets under the tongue or in the pouche of one cheek where the tablet slowly dissolved. In contrast to the usual peroral method of enteral administration, we shall designate this as 'sublingual' in order to avoid confusion.

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[1] The preparations of estradiol and of anhydrohydroxyprogesterone were supplied by the Society of Chemical Industry, Ciba, Basle, Switzerland.

CASE REPORTS

Case 1. K. S., 50 years old; gravida 2, para 2, menarche at 12 years of age. Menstrual periods occurred every 4 weeks, lasting 4 to 5 days, and were of average intensity. For some months there had been metrorrhagia, an endometrial biopsy showing glandular hyperplasia. Repeated roentgen treatment had been given (each time about 90 r) which stopped the hemorrhage. Patient complained of tiredness, outbreaks of sweating, and itching of the external genitals. From April 14th to 28th, 1942, the patient received daily 6 tablets sublingually, each containing 1 mg. of estradiol, a total of 90 mg. Endometrial biopsy on April 28th showed proliferation of the mucosa. The patient then received from May 1st to 3rd and from the 9th to 12th, 5 mg. of anhydrohydroxyprogesterone in tablet form sublingually, a total of 150 mg. Biopsy of the endometrium on the 28th day of the cycle showed a transformation toward a secretory phase with glycogen deposits. On May 13th menstruation started which lasted for 5 days. Since then the patient has remained free from complaints.

Case 2. W. F., 55 years old; gravida 12, para 7; menarche at 16. Menstrual periods occurred every 3 weeks lasting 6 to 7 days, very profuse. A curettage was performed in 1939 because of meno-metrorrhagia which had persisted for a year. The histological diagnosis was a glandular cystic hyperplasia of the endometrium. In consideration of the patient's age, a single treatment with roentgen ray (approx. 230 r per ovary) was given. There has been no hemorrhage since July, 1939. During the last few months the patient complained of hot flushes and insomnia.

From April 17th to May 1st, 1942, the patient has taken daily 5 tablets sublingually each containing 1 mg. of estradiol, i.e. a total dose of 75 mg. within a period of 15 days. The endometrial biopsy on May 2nd showed that the uterine mucosa was in the proliferative phase. From May 6th to 11th, 1942, the patient received 5 tablets sublingually of anhydrohydroxyprogesterone, i.e. 150 mg. within 6 days. The patient began to menstruate on the 26th day of the cycle (May 12th). The endometrial biopsy made on the same day showed some secretory transformation with glycogenic deposits in the glands; menstrual disintegration of the mucous membrane was the predominant characteristic. Menstruation lasted from May 12th to 16th, was of medium intensity and stopped spontaneously. Hot flushes and insomnia disappeared.

Case 3. W. R., 52 years of age; para 2; menarche at 16. Menstrual periods had occurred every 4 weeks lasting 4 to 5 days, and were fairly profuse. Curettage was performed in 1939 because of metrorrhagia. Glandular hyperplasia (histologically confirmed) recurred soon afterwards. The patient received roentgen-ray treatment with approximately 230 r per ovary. This patient also complained of mild ovarian deficiency symptoms.

The patient received 4 tablets of estradiol sublingually daily from April 18th to May 2nd, 1942, i.e. a total of 60 mg. An endometrial biopsy made on May 4th showed a proliferative endometrium. From May 6th to May 11th 5 tablets sublingually per day of anhydrohydroxyprogesterone were administered. On May 13th, the 26th day of the cycle, bleeding occurred. A biopsy made on the same day showed the endometrium in a state of menstrual disintegration. The bleeding stopped after 4 days, on May 16th. The patient stated that she 'felt better.'

Case 4. B. S., 48 years of age; menarche at 14. The menstrual periods recurred every four weeks, lasting 9 days, and were fairly profuse. There had been two abortions and no normal birth. Meno-metrorrhagia had persisted for 6 months. Endometrial biopsy showed glandular hyperplasia of the endometrium. The patient then received a single roentgen-ray treatment, approximately 240 r per ovary. Soon afterwards mild headache, hot flushes and temporary pruritus occurred.

From April 18th to May 2nd, 1942, the patient received daily 4 tablets of estradiol sublingually, i.e. a total of 60 mg. within 15 days. Biopsy made on May 5th showed a proliferative endometrium. From May 6th to May 11th, the patient received sublingually 5 tablets of anhydrohydroxyprogesterone, i.e. a total of 150 mg. within 6 days. On May 12th, the 25th day of the cycle, bleeding started, lasting for 3 days, and then ceased spontaneously. This patient was particularly benefited by the treatment, as all previous complaints such as headache, hot flushes and itching disappeared.

Case 5. W. B., 48 years old; para 2; menarche at 15. Menstrual periods recurred every 3 to 4 weeks lasting for 8 days, and were very profuse. At 17 there had been juvenile bleedings. Since 1938 she had had meno-metrorrhagia. This had increased in severity during the last few months of 1939. The patient was curetted in December, 1939, and the diagnosis was that of glandular cystic hyperplasia. She then was given a single treatment of 240 r per ovary. No hemorrhages have occurred since, but there have been headaches, outbreaks of sweating and debility.

The patient received sublingually, daily, from April 19th to May 3rd, 1942, 5 tablets of estradiol, i.e. 75 mg. within 15 days. Endometrial biopsy on May 4th showed that the endometrium was in the proliferative stage. From May 9th to May 14th, 1942, the patient was given sublingually daily 5 tablets containing 5 mg. anhydrohydroxyprogesterone, i.e. 150 mg. within 6 days. The endometrial biopsy made on May 15th (the 27th day of the cycle) showed a fully developed secretory phase with glycogen deposits in the glands. Bleeding continued subsequently until May 20th when menstruation ceased. The patient stated that she felt better after treatment.

Case 6. S. W., 51 years of age; menarche at 13. Menstruation occurred every 4 weeks, and was profuse, lasting 5 to 6 days. There had been 6 normal pregnancies. For the last year the patient had had irregular, profuse menstruation. Endometrial biopsy in 1939 showed glandular cystic hyperplasia. After a single roentgen-ray treatment of approximately 230 r per ovary, the hemorrhages ceased. The patient still suffered, however, from hot flushes, headache and articular pain.

From April 20th to May 4th, 1942, the patient received sublingually 4 tablets of estradiol daily, i.e. 60 mg. within 15 days. Endometrial biopsy on May 5th showed the proliferative phase. From May 11th to May 16th she received daily 25 mg. of anhydrohydroxyprogesterone sublingually in the form of tablets i.e., a total of 150 mg. Menstruation, lasting for 3 days started on May 17th. The patient's complaints were relieved.

Endometrial biopsies following treatment with doses of 60, 75 or 90 mg. of estradiol in the form of tablets prepared for use sublingually, show the proliferative phase in endometrium of the human female after roentgen therapy. This fact seems to be all the more important as Reifferscheid and Schmidt (4) required, in the case of a female castrate, 300 to 400 mg. of a glucoside compound of estradiol by ordinary peroral administration to induce the proliferative phase in the endometrium, but only 150 to 195 mg. of estradiol in alcoholic solution on sublingual administration. Herrenberger (3) also reports transformation of the endometrium in a female castrate after the sublingual administration of 180 mg. of estradiol in alcoholic solution. We obtained the same effect with estradiol in the form of specially prepared tablets for sublingual administration with one-half to one-third of the dosage employed by the above workers (fig. 1).

The ratio between the sublingually active dose of estradiol and the injection dose of estradiol dipropionate is between 2 and 3:1 as we have always produced endometrial proliferation in a female castrate by the injection of 25 to 30 mg. of estradiol dipropionate.

Further, a transformation of the endometrium of a female castrate toward the secretory phase has been obtained with 150 mg. of anhydrohydroxyprogesterone in the form of tablets, especially prepared for sublingual administration.

In a previous paper (7), we were able to show that the secretory phase in the endometrium with subsequent menstruation, after previous proliferation, could be effected by the peroral administration of 220 to 300 mg. of anhydrohydroxyprogesterone in women who had received roentgen-ray therapy some years before. This was 5 to 8 times as high as the dose of progesterone required by injection. By sublingual administration, the same effect can be obtained with about 3.5 times the injected dose (fig. 2).

With reference to the mechanism of the hormone action after sublingual application, the advantage of

this method of medication is based on the particularly favorable conditions of absorption from the oral mucous membrane, whether it is via the blood stream (8) or via the lymph passages (9). Following the ingenious investigations of Pedersen-Bjergaards (10) it has been shown that 90 per cent of estrone absorbed through the portal vein is inactivated by the liver.

The explanation for the discrepancy between the dosage of estradiol which has been found effective in these investigations and those of Herrenberger, Reifferscheid and Schmidt is probably to be found in the different method of preparation and administration of the same hormonal substance. Whereas the latter workers employed alcoholic solutions, we used the tablets especially prepared for sublingual administration, as already mentioned. These contain the hormone in the form of an aromatic melted mass, compressed into tablets under heavy pressure; they slowly dissolve in the saliva and are uniformly absorbed. The superiority of these tablets as regards absorption is seen from the detailed experiments of Wattenwyl (11) to which we would particularly refer.

After the dosage of estradiol and anhydrohydroxyprogesterone had been determined in patients with castration symptoms who had had roentgen therapy, a number of patients with other gynecologic disorders were treated. Detailed clinical reports of these cases are being published elsewhere and only a few examples are briefly mentioned here. These cases are cited to show not so much the success of treatment as the efficacy of the sublingual method of application of the female sex hormones.

Nine cases of secondary amenorrhea of 3 to 15 months' duration were treated, the age range wa 17 to 27 years. In 6 cases, menstruation was effected after 3 to 6 months of treatment. Two of the patients unfortunately failed to return after beginning treatment. In one patient no menstrual period has yet occurred in spite of two series of treatments. The patients who were successfully treated received sublingually doses of 30, 44 and 75 mg. of estradiol, respectively, in the form of tablets. This amount of hormone produced proliferation of the endometrium. Subsequently, doses of 75, 100 and 150 mg. of anhydrohydroxyprogesterone sublingually in the form of tablets produced the progestational effect with menstrual bleeding.

CASE REPORT

Patient T. E., was a 35-year old female with acromegaly who had had amenorrhea for 4 months, and prior to that time oligomenorrhea. Roentgenograms showed an enlargement of the sella turcica. There was amblyopia in the left eye. Considerable enlargement of the extremities had occurred. The basal metabolism had increased +32%. A moderate amount and normal distribution of pubic hair were present, the vagina was narrow but smooth. Portio was of normal height; the collum anteverted. The uterus was anteflected, smaller than normal, firm, easily movable; adnexa free. The endometrial biopsy showed an atrophic mucosa.

Treatment. A total of 75 mg. of estradiol was administered sublingually in the form of tablets over a period of 15 days. Biopsy showed proliferation of the endometrium. Bleeding started 48 to 72 hours after discontinuation of treatment, lasted for 13 hours, and ceased following three intramuscular injections of 1 mg. of estradiol dipropionate. A full course of treatment was then given sublingually using 60 mg. of estradiol and 150 mg. of anhydrohydroxyprogesterone, both in the form of tablets. Menstrual bleeding occurred from the 26th to the 28th day of the treatment cycle. The patient stated that she no longer suffered from the troublesome headaches after the menstruation.

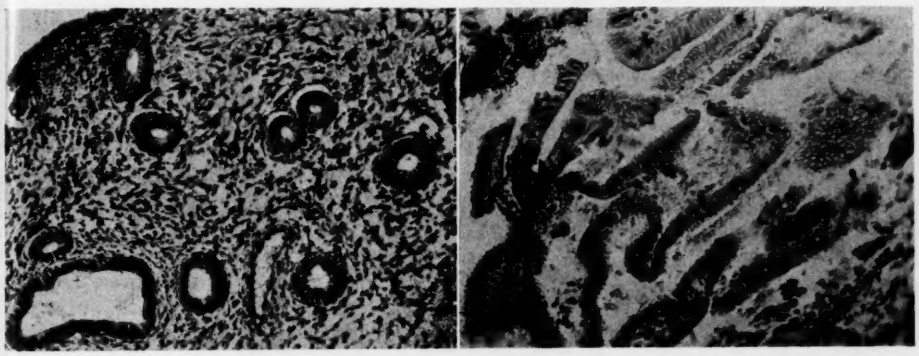

Fig. 1. TISSUE OBTAINED BY ENDOMETRIAL BIOPSY of a patient treated with 60 mg. of estradiol sublingually in the form of tablets showing the endometrium in the proliferative phase.

Fig. 2. TISSUE OBTAINED BY ENDOMETRIAL BIOPSY of a patient treated, after estradiol priming, with 150 mg. of anhydrohydroxyprogesterone sublingually in the form of tablets showing the endometrium in the early secretory phase.

A second cycle of treatment sublingually with 75 mg. of estradiol in 9 days and 25 mg. of anhydrohydroxyprogesterone daily for 6 days, a total of 150 mg. was followed by bleeding on the 21st day lasting 5 days. A third course of treatment with anhydrohydroxyprogesterone alone was begun 12 days after menstruation had ceased. After a total of 75 mg. in 5 days bleeding occurred which lasted 4 days.

Up until the present time there has been relief from headache, although the objective state is unchanged.

A further series of 18 cases with various indications for therapy, such as glandular hyperplasia of the endometrium, threatened abortion, hypoplasia with oligomenorrhea, dysmenorrhea and climacteric deficiency symptoms were treated alternating the two sex hormones which were administered sublingually. The impression was gained that this much simpler and more pleasant method of administration of the hormones is not inferior in action to treatment by injection. Because of the particularly favorable conditions for sublingual absorption this may become the method of choice for treatment in the future.

SUMMARY

Six women who had received roentgen-ray treatment of the ovaries in 1939, were treated with 60, 75 or 90 mg. of estradiol sublingually. Proliferation of the endometrium was produced. By subsequent sublingual administration of 150 mg. of anhydrohydroxyprogesterone secretory changes in the endometrium were obtained. The characteristics of proliferation and secretion were verified by endometrial biopsy and histological examination.

The mode of sublingual application of the female sex hormones is briefly discussed and a few clinical examples given.

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A Case of Delayed Induction of Menstruation in Primary Amenorrhea

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A 23-YEAR-OLD white woman, married for 2 years, was referred in March, 1935, for sterility. The patient had never menstruated. She had married at 21 years of age. Still having complete amennorhea 6 months later she consulted a physician who prescribed theelol and chorionic gonadotropin. This was taken for 3 months without results.

The mother had not menstruated until she married, then only at irregular intervals, and there had been only one pregnancy. The patient's personal history was not remarkable. She stated that she felt well except for frontal headaches which occurred frequently when she was excited or tired. She fatigued easily.

Physical examination revealed an attractive young woman of boyish figure whose height was 64.8 in. and weight 117.7 lbs. There was only slight mammary development. The pubic hair had a tendency towards masculine distribution. The axillary hair was abundant, and there was a sufficient excess of facial hair that treatment for its removal at regular intervals by electrolysis was required. Skiagrams of the skull showed nothing abnormal. Vaginal examination revealed a small uterus, and the ovaries could not be felt on bimanual examination.

The laboratory findings (blood and urine) were within the normal range. There was a daily excretion of 25 M.U. of estrogen and 7 to 8 mg. of 17-ketosteroids as measured by the photoelectric colorimeter. Repeated basal metabolic-rate determinations gave values from 60 to 90 per cent of normal, averaging about 80 per cent. Blood pressure readings taken at the same time were as follows: 108/72, 98/60, 100/62, 112/82 mm. Hg.

Anthropomorphic measurements were: bust 30.3 in., waist 25.3 in., hips 35.2 in., height to symphysis 33.3 in., height 64.7 in., span 63.8 in.

The patient was given thyroid therapy[1] starting at 1 grain and gradually increasing to 3 grains daily. She was also given 1 cc. of anterior pituitary extract[2] daily and 1 cc. of theelin[3] every other day for two-week periods during the next year. No noteworthy change occurred except that she lost the tired feeling, the breasts increased slightly and the hips markedly in size. The measurements were: waist 25.3 in., bust 30.7 in. and hips 37.6 in. There was also some growth of the uterus but the ovaries were still not palpable.

On Sept. 11, 1936, she was given pregnant-mare serum[4] intramuscularly, 5 units daily, in the thighs. One week later this was increased to 10 units. This dosage caused an intense local reaction with redness and swelling, and the inguinal glands became swollen and tender. The dosage was reduced again to 5 units daily, alternating the legs as the site of the injection. After two weeks the swelling which occurred with each injection ceased and did not recur. One month later, in October, each ovary was barely palpable. On November 30 both ovaries were enlarged and tender. Measurements at this time showed: waist 26.0 in., bust 31.5 in. and hips 38.2 in. The dosage of pregnant-mare serum was increased to 10 units daily for two weeks and then a rest period of two weeks was interposed. On December 14 both ovaries were found to be enlarged, easily palpable and tender. The following month each was the size of a large walnut and very tender. The dosage was decreased to 5 units daily. This treatment was continued with injections at two-week intervals until October, 1937, when therapy was discontinued, the ovaries then being the size of a plum and still very tender. It was believed that the ovaries had become cystic and that further medication was inadvisable. The following April, 1938, a final checkup showed that the ovaries had decreased in size and were no longer tender.

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[1] The desiccated thyroid was supplied by Armour & Co., Chicago, Ill.

[2] The anterior pituitary extract was that of E. R. Squibb & Sons, New Brunswick, N. J.

[3] The estrogen (Theelin) was manufactured by Parke, Davis & Co., Detroit, Mich.

[4] The pregnant-mare serum (Gonadogen) was supplied by the Upjohn Company, Kalamazoo, Mich.

Nothing further was heard from the patient until Sept. 24, 1939, when she first menstruated, having a normal period lasting 5 days. There was a second period from November 2 to 7 after a 39-day interval. A third period of flowing occurred from November 18 to 24 and the periods were regular during December, 1939, and January and February, 1940.

In February, 1941, she reported that she had not menstruated since the preceding February. An examination at this time showed that there had been a decrease in the bust measurement to 30.9 in. and in the hip measurement to 37.2 in. The facial hair was somewhat more prominent. The ovaries were no longer palpable. The basal metabolic rate was 75 per cent of normal. Treatment with pregnant-mare serum was resumed at 10 units three times weekly, after a preliminary test for sensitivity. After the first two injections the inguinal glands became swollen and tender, but there was no inflammation at the site of the injection. This condition subsided after the omission of one injection and did not recur. Thyroid was again given, 2 grains daily. After 4 months of treatment at 2-week intervals the bust measurement had increased to 33.0 in. and the ovaries had become enlarged and slightly tender. Treatment was continued until December, 1941. During January, 1942, there was a slight flowing lasting 2 days. At this time the injection of pregnant-mare serum was followed by two weeks' treatment with 1 mg. of progesterone every other day for 8 doses. No period occurred in February or March, and all medication except thyroid was discontinued on March 16, 1942. A regular menstrual period lasting 5 days began on April 20, 1942.

Vaginal smears made twice weekly during the past year showed a regular increase in estrogenic action during each period of medication. No endometrial studies were made

The following is offered as a possible explanation of the long delay in the appearance of the menstrual periods which began two years after medication was stopped. The action of the pregnant-mare serum caused an increase in follicle maturation but the follicles failed to rupture. This resulted in a condition of cystic ovaries. After cessation of medication the cysts slowly regressed until a balance was reached between waves of follicle maturation and regression; at this point menstruation occurred. The recurrence of menstrual periods after a second course of treatment lends weight to the assumption that menstruation was the result of the effect of the medication on the ovaries.

SUMMARY

The case is reported of an amenorrheic young woman who gave no immediate response to treatment with pregnant-mare serum but who began to menstruate for the first time two years after cessation of the treatment. After another amenorrheic period of a year, menstruation again occurred following treatment with the serum and desiccated thyroid as adjuvant.

Observations on the Mechanism of Uterine Bleeding

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AN INTELLIGENT therapeutic approach to the problem of menometrorrhagia will result only when the mechanism of uterine bleeding is fully understood. The artificial induction of pseudomenstrual bleeding in the castrated human female clarifies many controversial points. The data on the case to be reported has been charted in figure 1.

CASE REPORT

Z.M.D., a white female, 28 years of age, presented herself at the Endocrine clinic of the University Hospital during the latter part of 1939 complaining of severe menopausal symptoms. One year previously she had been submitted to laparotomy and both fallopian tubes and ovaries were removed because of tubo-ovarian abscesses. From Nov. 14 to 16, 1939, a 48-hour urine specimen was obtained and the urine was found to contain an insufficient amount of estrogen for assay. The vaginal smear revealed a castrate or 1+ reaction. A curettage was performed on Nov. 16, 1939 and no endometrium could be obtained. From December 7 to 22 the patient was given 1 mg daily of diethylstilbestrol[1] orally, during which time she noted that the breasts had become full, libido had increased, the hot flashes were ameliorated and the vaginal smears revealed a 3+ reaction. Beginning on December 18 she received 10 mg. of progesterone[2] parenterally per day for 4 days. Uterine bleeding began on December 26, and a thorough curettage was made one hour after onset. No tissue could be obtained, The curette felt gritty on scraping it against the wall of the uterine cavity. Bleeding lasted 3 days. One mg. daily of diethylstilbestrol orally was again administered from Dec. 29, 1939 to Jan. 22, 1940. Beginning on January 19 she received 10 mg. of progesterone daily for 3 days. A suction curettage was performed on January 24 and no endometrium was obtained. Bleeding started 2 days later and lasted 5 days. During February, 1940, she had two short courses of diethylstilbestrol (fig. 1) and in March, 1940, she received along with the diethylstilbestrol therapy 8 injections of 10 mg. each of progesterone. Following cessation of therapy the patient was hospitalized to await the onset of bleeding. This occurred 2 or 3 days later and within a few hours of its onset a thorough dilatation and curettage was performed under anesthesia. Histologic sections of the material obtained on this occasion, as on other occasions, revealed only blood clot, fibrin, some endocervical mucous glands and/or cervical epithelium but no endometrium.

Bleeding episodes were induced on several other occasions following estrogen-progesterone therapy. Progesterone alone proved ineffective, for progesterone withdrawal bleeding could not be induced unless there was priming by estrogens or the simultaneous administration of estrogens and progesterone.

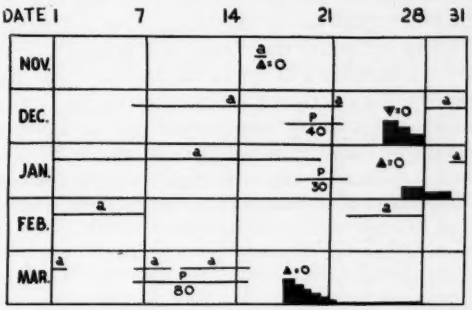

FIG. 1. INDUCTION OF UTERINE BLEEDING IN A CASTRATED FEMALE. *Triangle*, dilatation and curettage; *inverted triangle*, suction curettage; *O*, no endometrium obtained; *a*, 1 mg. of oral diethylstilbestrol per day; *p*, parenteral progesterone in 10 mg. doses.

This case study is enlightening for it emphasizes that menstruation is not to be considered as a 'kind of abortion of the embedded unfertilized ovum' as defined by Powers in 1821. This long-accepted tenet has been proven unacceptable since endometrial studies have revealed that anovulatory bleeding is not an uncommon occurrence. The endometrium mirrors ovarian activity and the rôle played by the endometrium is only contributory and not of primary importance. Uterine bleeding may occur from a progestinal, a hyperplastic, a persistent estrogenic or an atrophic endometrium. In this case thorough curettage yielded but the minutest amount of scrapings and the tissue obtained was not endometrial but was from the endocervix. The failure to obtain sufficient endometrium within one hour after onset of flow for study on 3 occasions following massive doses of estrogen and progesterone therapy, is sufficient evidence of the minimal rôle

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[1] The diethylstilbestrol was supplied by Eli Lilly and Co., Indianapolis, Ind.

[2] The progesterone (Lutocylin) was supplied by Ciba Pharmaceutical Products, Inc., Summit, N. J.

played by the endometrium in bleeding. Sudden withdrawal of estrogen-progesterone therapy was followed on several occasions by a menstrual flow but bleeding did not occur subsequent to withdrawal of large doses of progesterone (50–80 mg.) alone. These findings substantiate the contention that menstruation is the result of a sudden deprivation of estrogen or of progesterone in the presence of estrogen and that pathologic bleeding is based on the same mechanism of fluctuating levels of ovarian hormones. There is, therefore, no distinction between menstrual bleeding and menometrorrhagia. This case study, on the basis of proven insufficiency of the endometrium further emphasizes and confirms the observations of Bartelmez (1) that the myometrium and its vascular supply are dependent upon endocrine control and are responsible for uterine bleeding. Bartelmez believes that the explanation for the reduction or stoppage of the flow of blood to the mucosa must be sought for in the myometrium and not in the endometrium. The perivascular interlacing arrangement in the uterine muscle makes it easy to understand that the degree of contraction and relaxation of these muscle bundles may have much to do with regulating the duration and amount of menstrual bleeding. Excessive uterine bleeding will occur if the proximal (myometrial) portion of the spiral arterioles fails to constrict or be constricted, following the initial extravasation of blood distally. Menstruation is fundamentally a vascular phenomenon in which the endocrines play the underlying rôle.

CONCLUSIONS

1. With estrogen-progesterone therapy uterine bleeding could be induced at will in a young female, surgically castrated one year previously. When progesterone alone was administered, bleeding did not follow.

2. Failure to obtain endometrium on thorough curettage before and after therapy indicated complete atrophy of the endometrial lining.

3. The hormonal induction of bleeding to simulate a menstrual episode on three occasions in this patient would appear to emphasize the importance of the myometrium and its vascular supply and the minimal rôle played by the endometrium in this bleeding.

REFERENCE

1. Bartelmez, G. W.: Glandular Physiology and Therapy. Menstruation. *J. Am. Med. Assoc.* 116: 702. 1941.

A Case of Schizophrenia in a Hypogonad Man

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The schizophrenic psychosis presents numerous features suggestive of psychosexual immaturity. Usually, however, the patients are not remarkable for evidences of somatic sexual abnormality. Likewise, attempts to treat the psychosis with androgens have not, in our hands at least, given consistently favorable results. Possibly the failures in the treatment may be due to reduced reactivity to the hormone. Since eunuchs and eunuchoids are notably more responsive to androgens than are normal individuals, it was a matter of interest when opportunity arose to study an individual who was both eunuchoid and schizophrenic—a rare combination.

Case Report

The patient, *H.J.*, was an unmarried, 44-year-old man of Scotch-Irish extraction, who entered the Worcester State Hospital on first admission Dec. 31, 1941.

The family history was scanty and not relevant to the current problem.

As to personal history, the patient was born by normal delivery after a normal pregnancy. As a little boy he had been 'puny.' He had had severe pneumonia at 2, and the 'usual children's diseases' without known sequelae. In childhood he was regarded as a 'sissy,' being much addicted to crying. His school life was undistinguished and he showed little ambition. The voice failed to change at adolescence. He was rejected by the army in 1917 because of what was diagnosed as 'hernia.' The right testis was removed at 34 but the reason could not be determined. It was reported that he became fat following the operation. Some heterosexual interest was claimed and two amorous affairs with women were reported. Most of his recreational time, however, was spent with men and there were suggestions in the history of homosexual attachment.

His industrial history indicated mediocre ability and energy but dependability and stability.

The date of onset of the psychosis could not be precisely determined. In July, 1941, the patient began complaining because he had to work at night and because his helper was very lazy. Little things began to irritate him. His family physician was consulted and advised him to take a temporary rest. Shortly afterwards he began to have crying spells and complained that the food was of poor quality and that the landlady and his fellow-boarders were irritating. He felt that his fellow-workmen were deliberately persecuting him. He was told by his physician that he was going through a masculine equivalent of the menopause.

Upon admission to the hospital in December, 1941, he was found to show stereotyped, odd, manneristic behavior. His emotional reactions were shallow, inappropriate and little influenced by external circumstances. His associations were fragmentary and his speech irrelevant and incoherent with frequent use of neologisms. He was suspicious and somewhat grandiose but rather noncommittal in discussing his delusions. His judgment was poor and he was completely lacking in insight regarding his illness. The diagnosis was schizophrenia, '*other types*' —*i.e.*, not conforming consistently to any of the Kraepelinian sub-types.

Physical examination revealed that he was tall, well-developed, and slightly over-weight. He was prematurely gray and the body hair was sparse. The escutcheon was of the feminine type, as was the fat distribution. The voice was high-pitched. Slight varicosity of the veins of the legs was recorded. The right testis was absent and the left was notably hypoplastic, as was also the prostate.

Laboratory examinations showed normal blood pressure, pulse rate and rectal temperature. The oxygen-consumption rate could not be accurately determined because of poor co-operation, but a downward trend suggested that the true basal metabolic rate was probably low. The urine volume was somewhat scanty, the range for 24-hour samples being from 680 to 1580 cc. The creatine output was zero in 3 of 4 collections—a subnormal rate for a schizophrenic. The creatinine output was normal, ranging from 0.913 to 1.211 gm./24 hr. The total nitrogen per 24 hours was definitely low, ranging from 4.63 to 7.35 gm. The 17-ketosteroid output, as determined by the electrocolorimeter, ranged from 5.7 to 7.8 mg./24 hr., which was definitely low as compared with our findings in normal subjects and in most schizophrenics. The blood nonprotein nitrogen was 33.3 and the uric acid 2.26 mg./100 cc. The results of the blood study were normal except for an erythrocyte count of 4,410,000. The glucose tolerance was high, a low flat curve being obtained after the ingestion of 100 gm. of glucose. He also showed low reactivity to insulin, the drop at one hour being only 16 mg. per

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cent following intravenous administration of 0.1 u per kg. The blood sugar and blood pressure reactions to adrenalin were both normal.

The diagnostic impression was that the patient was certainly hypogonad. The downward trend of the oxygen consumption rate, the scanty urine, the reduced nitrogen turnover, the secondary anemia, the flat sugar curve and the history of long-standing lack of vigor were thought not to be accounted for, however, by the hypogonadism alone. They were tentatively ascribed to functional hypothyroidism.

Beginning at the end of January, 1942, a therapeutic test was begun with desiccated thyroid,[1] 2 grains daily. At the end of a week the patient had lost 8 pounds of weight and the pulse rate had risen to 90 to 100 per minute. The thyroid was therefore discontinued. The only apparent clinical effect of the material was an increase in excitability. The patient became increasingly elated, frequently pirouetted about the ward for minutes at a time, and often pretended to lead the orchestra while the radio was playing. His speech became increasingly fragmented, practically to the point of 'word salad.'

The attempt at metabolic stimulation was then given up and on February 10, methyl testosterone[2] in dosage of 10 mg. 3 times a week by mouth was begun. A period of 'hypomanic' behavior with aggressiveness towards attendants and visitors and the necessity for cold-sheet packs ensued. This development was probably in part a carry-over from the previous reaction to thyroid. The methyl testosterone was then discontinued until February 24, following which it was resumed at 10 mg. daily for 2 weeks. The patient was still over-active, requiring sedative hydrotherapy. He then began to improve clinically, and by March 5, was considerably quieter and less active, quite cooperative, friendly and good-humored. He seemed to understand what was said to him but his replies were so complicated by neologisms as to be unintelligible. He had become more careful about his personal appearance. He was detected masturbating.

On March 10 the methyl testosterone was increased to 10 mg. twice daily and on the 23rd, to 3 times daily, with 1 grain of desiccated thyroid added in the hope of increasing the reactivity to the androgen. The patient again became over-active and aggressive, requiring wet-sheet packs, so that on April 6 the thyroid was again discontinued. Ten days later he was quieter and was showing a slight gain in weight. He impressed the psychiatrist as beginning to show considerable homosexual interest in other patients.

Laboratory re-tests during the week of March 21 showed a doubtful increase in the oxygen-consumption rate, slower pulse rate, marked decrease in dextrose tolerance and moderate reduction of insulin tolerance. Other findings, and notably the 17-ketosteroid output, were not significantly altered.

The methyl testosterone was discontinued on April 21. At this time he was showing marked improvement. A week later he was normally quiet and was talking sensibly in a business-like, matter-of-fact way. He had entirely given up the use of neologisms and was working well on a farm crew. He spent much of his time when on the wards in reading.

On May 1 a subcutaneous implant of testosterone was made, 2 pellets of 75 mg. each being inserted. The improved status continued, he being apparently entirely free of the psychosis except for a certain residual amount of underlying suspiciousness and lack of insight. His relatives commented on a remarkable improvement in his personality, stating that he was now as normal as he had ever been.

On May 25 he was dismissed on indefinite visit in care of his family. The closing note comments on his beard's having become slightly heavier and his voice somewhat deeper.

On June 28 the patient returned unaccompanied to the hospital for a re-check. He looked well and was in good spirits. He was planning to resume regular employment in the near future. He was well-composed and rational and showed no apparent signs of psychosis.

SUMMARY

The case is reported of a middle-aged eunuchoid who had developed a schizophrenic psychosis. Following the use of methyl testosterone he made a striking recovery from the psychosis and, under the influence of a testosterone implant, at the time of report, had maintained the improvement for two months.

[1] The desiccated thyroid was supplied by the Armour Laboratories, Chicago, Ill.

[2] We are indebted to Dr. Erwin Schwenk of the Schering Corp., Bloomfield, N. J., for the androgen preparations which were used in this case.

Influence of Methyl Testosterone on Muscular Work and Creatine Metabolism in Normal Young Men[1]

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THERE HAS LONG been a common belief that male sex hormones are associated with muscular strength and endurance. A variety of evidence can be cited in general support of this belief. Increased strength and endurance is one of the most common subjective reports from male castrates and eunuchoids treated with testosterone. Treatment with androgens increased the voluntary activity of castrated male rats (1) and was reported to increase working capacity in adult patients with subnormal or absent testicular hormone production (2). There are numerous reports of the effects of testosterone on nitrogen and creatine metabolism in both eunuchoid and normal men; these suggest a fundamental influence on muscle metabolism and work which has been assumed to be associated with the androgenic activity of the compound. In view of these facts, it is reasonable to inquire whether responses to fatiguing exercise may be altered in normal man by androgen administration. This is a report on the results of experiments on these questions, using methyl testosterone because of its relatively high androgenic effect when given by mouth.

SUBJECTS

Four healthy male medical students were studied; their ages were between 21 and 30 years. Throughout the experimental period of 11 weeks they maintained their ordinary work in the medical school and subsisted on their usual normal diet except that they ate a meat-free meal on the night before each weekly examination.

PROCEDURE

The experimental period lasted 11 weeks with examination each week. Collection of urine was started at 6 o'clock on the evening before each examination and was continued until a blood sample was obtained from the subject in the fasting state on the following morning. After this blood sample was taken each man tested his grip strength 5 times with a standard hand dynamometer and the average of the two highest readings was recorded. Each man then ran for 2.5 minutes at a speed of 7 miles per hour on the motor-driven treadmill set at an angle of 10 per cent climb (vertical climb at 0.7 miles per hour). Blood samples were taken at 8 and at 15 minutes after the cessation of work. Urine collections were made covering the first, second, and third hours from the start of the exercise.

The experimental room was maintained at 78°F., humidity 45 to 55 per cent relative saturation, at all times. All blood samples were drawn from an arm vein, with a minimum of stasis. Blood was received in ice-cold tubes; potassium oxalate was used as anticoagulant.

After two weeks for control observations medication was begun. Two men received five 10-mg. tablets of methyl testosterone daily while the other 2 men received a like number of placebos made in the same mold. The tablets were taken one after each meal and two on retiring. After 4 weeks the groups were reversed without the subjects' knowledge; the men originally receiving the placebos were now given methyl testosterone and the other pair received placebos. After 3 weeks on this regime the dose was raised to 200 mg. of methyl testosterone per day for one week. During the last week of the experiment no medication was given.

It was expected that the methyl testosterone might cause increased creatine storage as had been reported for eunuchoids (3), castrated animals (4), and mature, male rabbits (5) after administration of testosterone. Accordingly, creatine hydrate was administered in capsules containing 250 mg., 4 times a day from the beginning of the fourth week to the beginning of the last week.

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[1] This work was supported in part by a grant from the National Research Council to one of us (A. K.). Valuable assistance was rendered by the Work Projects Administr tion, Official Project 65-1-71-124, sub-projects Nos. 343 and 380. Roche-Organon Inc., Nutley, N. J., and Schering Corp., Bloomfield, N. J., generously supplied the methyl testosterone tablets and placebos.

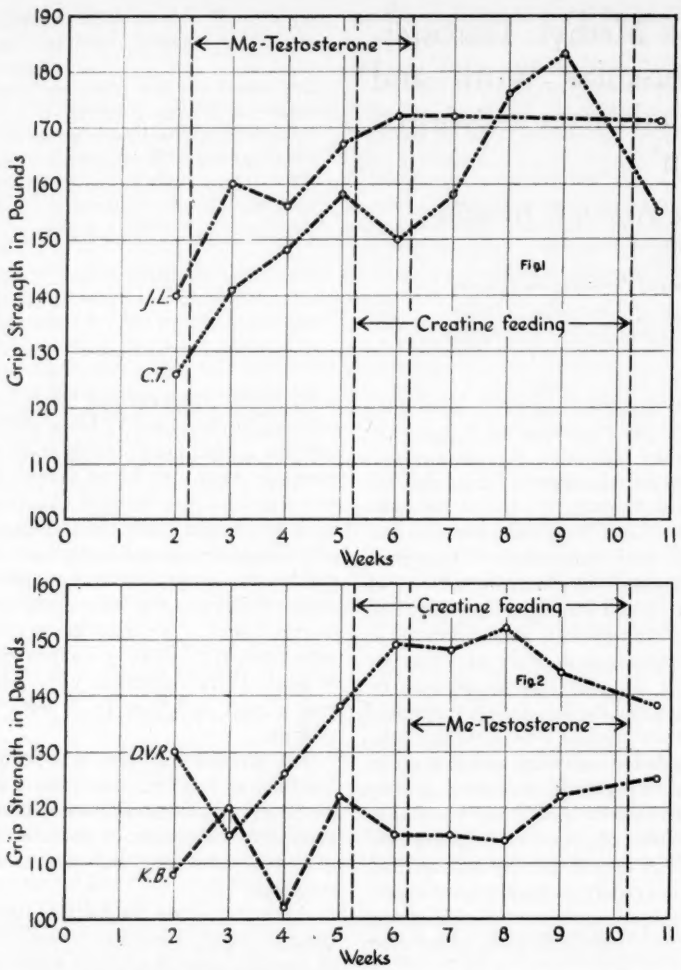

Fig. 1. GRIP DYNAMOMETER TESTS on subjects receiving methyl testosterone during the first part of the experimental period.
Fig. 2. GRIP DYNAMOMETER TESTS on subjects receiving methyl testosterone during the latter part of the experimental period.

Basal metabolism was measured on all subjects on the morning of each experimental day in the eighth, ninth and tenth weeks.

METHODS

Urine samples were analyzed for total nitrogen, creatine and creatinine. Nitrogen was estimated by the Kjeldahl procedure. Folin's modifications of the Jaffe reaction were used for creatine and creatinine estimations in blood and urine.

Blood lactate was measured by Edward's (6) modification of the method of Friedemann, Cotonio and Shaffer (7). Pyruvate in the blood was estimated by a modification, partly suggested by Dr. E. S. Guzman Barron, of the method of Lu (8). Lactate and pyruvate in the blood were stabilized with fluoride and iodoacetic acid.

Blood sugar was estimated by the method of Folin (9). Hemoglobin was measured photoelectrically.

RESULTS

Muscular work and ability. Subjective reports and simple observation disclosed no effects of the hormone administration on physical vigor. Diaries were kept by the subjects. Two of the men recorded a general sense of euphoria which coincided with the period of methyl testosterone administration and one of these men recorded the disappearance of the euphoria when the hormone was withdrawn and placebos were substituted. Aside from a slight train-

ing effect, there was no change in the sense of effort and fatigue in the exercise tests.

The grip-strength tests in 3 men showed a moderate tendency to improve independently of the methyl testosterone administration. The fourth subject showed little change in this score throughout the entire experimental period. Figures 1 and 2 clearly depict the absence of any effect of the medication.

Brief severe work, such as the treadmill test used here, produces characteristic changes in the blood. Perhaps the best quantitative relations to muscular ability and fatigue are seen in the concentrations of lactate and pyruvate, and in the general blood concentration which can be followed by the increase in percentage of hemoglobin. The averages for these variables for two-week periods on each subject are tabulated in table 1. The severity of the work is shown by the magnitude of the changes induced in these variables. There is no significant effect of the administration of methyl testosterone on any of these variables, however, either in the changes from rest or in the indicated rate of recovery after exercise.

Creatine, creatinine and nitrogen metabolism. The concentration of creatinine and non-protein nitrogen in the blood remained very constant throughout the entire experimental period. The creatine concentration, however, showed a distinct tendency to rise during the period of medication in all 4 subjects. In the 2 men who first were given the methyl testosterone and then placebos, there was some tendency for the blood creatine concentration to return toward the pre-medication level when the drug was withdrawn, but the average values were still above 3 mg. per 100 cc. as long as 4 weeks after the last administration of methyl testosterone. The averages are shown in figures 3 and 4.

The most marked changes were seen in the urinary excretion of cretaine, which rose steadily in the period of administration of methyl testosterone and attained levels more than 5 times those of the control periods. Excretions of more than a gram per 24 hours were recorded in a number of instances. Upon change to placebos the urinary output of creatine promptly began to diminish and, in the 2 men who had been receiving placebos for the last 5 weeks of the experiment, the creatine output finally returned to the original control levels during the last week.

These changes in creatine excretion were not accompanied by corresponding changes in the excretion of either creatinine or total nitrogen. Creatinine excretion remained fairly constant. On the whole, total nitrogen excretion tended to diminish throughout the entire experimental period. Since the dietary nitrogen intake was not controlled adequately, it is not possible to ascribe any special significance to the nitrogen output. It is certain, however, that the total nitrogen excretion did not tend to parallel the creatine output. The average values for these urinary excretions are given in figures 5 and 6.

The administration of creatine hydrate during part of the experimental period may be considered to be a complicating factor. It is clear, however, that the

TABLE 1. CONCENTRATIONS OF BLOOD CONSTITUENTS PER 100 CC. EACH VALUE IN THE TABLE IS THE AVERAGE OF MEASUREMENTS FOR 2 WEEKS

Period, Weeks	Subject	Glucose, mg.			Hemoglobin, gm.			Pyruvate, mg.			Lactate, mg.		
		Rest	8 min.	15 min.	Rest	8 min.	15 min.	Rest	8 min.	15 min.	Rest	8 min.	15 min.
1–2	JL	96	123	115	14.4	15.7	15.3	1.1	3.8	4.9	9	76	83
3–4	JL	**87**	**94**	**94**	**14.5**	**15.6**	**15.2**	**1.0**		**4.5**	**10**	**96**	
5–6	JL	**96**	**100**	**100**	**14.4**	**15.4**	**14.9**	**1.6**	**4.9**	**4.7**	**11**	**122**	**79**
7–8	JL	86	100	92	14.3	15.4	15.2	1.3	4.4	4.1	10	92	66
9–10	JL	87	102	98	13.9	15.3	15.0	1.3	4.6	4.4	9	105	91
1–2	CT	99	122	135	14.3	15.3	15.1	0.8	2.8	3.4	8	86	92
3–4	CT	**129**	**121**	**117**	**14.1**	**15.1**	**15.0**	**0.8**	**3.1**	**3.8**	**11**	**100**	**75**
5–6	CT	**130**	**114**	**112**	**13.7**	**15.0**	**14.9**	**0.8**	**3.1**	**3.4**	**10**	**94**	**78**
7–8	CT	104	106	103	13.6	14.9	14.6	0.8	2.9	2.8	8	90	71
9–10	CT	115	117	110	13.4	15.4	14.6	1.1	3.3	3.3	10	87	79
1–2	DVR	94	114	113	14.0	15.3	15.0	1.1	4.0	4.7	8	90	63
3–4	DVR	103	90	87	14.1	15.3	15.1	1.0	4.4	4.0	12	108	73
5–6	DVR	90	99	90	14.3	15.4	15.0	0.9	4.0	4.0	10	90	76
7–8	DVR	**102**	**84**		**14.3**	**15.7**		**1.1**	**3.8**		**9**	**69**	
9–10	DVR	**85**	**100**	**95**	**14.2**	**15.4**	**15.1**	**0.9**	**3.1**	**3.3**	**11**	**90**	**80**
1–2	KB	109	119	108	14.8	16.1	15.7	1.3	3.7	3.8	12	110	111
3–4	KB	100	112	102	14.5	15.7	15.6	0.9	4.2	4.0	11	95	96
5–6	KB	97	113	108	14.7	16.0	15.7	1.2	4.2	4.0	11	94	88
7–8	KB	**114**	**119**	**117**	**14.6**	**16.0**	**15.4**	**1.0**	**4.5**	**4.3**	**10**	**98**	
9–10	KB	**80**	**108**	**105**	**14.5**	**16.2**	**15.0**	**1.1**	**4.1**	**4.5**	**13**	**116**	**91**

Figures in boldface are those obtained during the period of daily administration of methyl testosterone.

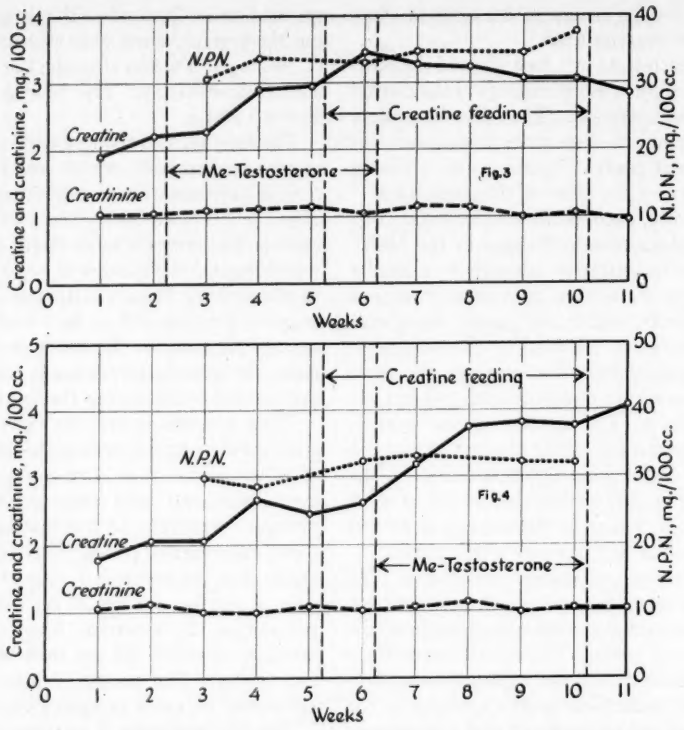

Fig. 3. BLOOD CREATINE, CREATININE AND NON-PROTEIN NITROGEN CONCENTRATIONS in subjects receiving methyl testosterone duri the first part of the experimental period.

Fig. 4. BLOOD CREATINE, CREATININE AND NON-PROTEIN NITROGEN CONCENTRATIONS in subjects receiving methyl testosterone duri the latter part of the experimental period.

extra creatine intake in itself did not provoke either creatinuria or creatinemia to any extent. So far as the data go it appears that the creatine ingestion had little or no effect on the concentration in either blood or urine. It may be noted that by the fourth week of administration of methyl testosterone the urinary output of creatine exceeded the extra creatine intake and that similar creatine output values were obtained whether creatine was fed or not.

Basal metabolism was substantially constant and was within normal limits at all times. With the exception of a single measurement on one subject all values on all 4 subjects were within the range −1 to −10 per cent in terms of normal averages for the respective ages and surface areas of the men, using the Mayo Clinic standards of Boothy and Berkson (10).

It is not necessary to present in detail the blood and urine concentrations of creatine, creatinine and nitrogen for the recovery period following the treadmill exercise. The results confirm the picture of moderate creatinemia and marked creatinuria obtained from the resting samples.

The rate of creatine output after exercise was reduced, as compared with that during rest, in all experiments; the work-recovery values in individu experiments ranged from 18 to 79 per cent of the pr ceding output in rest, with a grand average of 45 p cent. On the other hand, the rate of excretion creatinine in recovery was almost always increas the grand average being 11 per cent greater than rest before work. Likewise, the rate of total nitrog excretion was increased following work, the gra average being 23 per cent above the values in rest b fore the work. However, none of these changes recovery as compared with rest showed any ten ency to be affected by the medication.

DISCUSSION

The four men, two castrates and two eunuchoid studied by Simonson, Kearns, and Enzer (2) unque tionably improved in the physical tests during t period of administration of methyl testosterone. Ho ever, no adequate controls were provided, and t effects of learning and training could not be eval ated. Even if we agreed that methyl testosterone r sults in improved physical ability in cases of ma hormone inadequacy (which is not proved), it wou be uncertain what could be expected in normal m

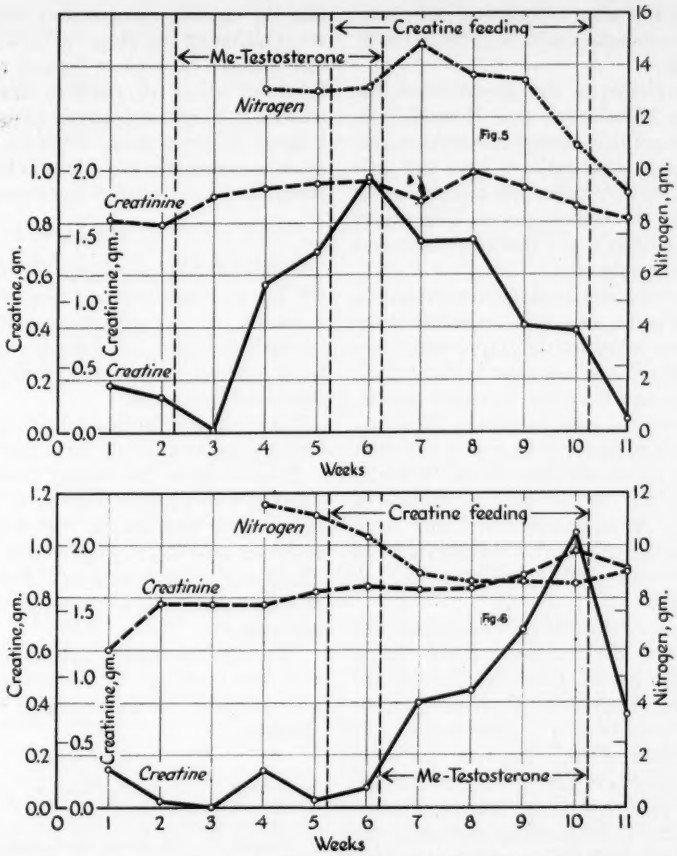

Fig. 5. CREATINE, CREATININE AND TOTAL NITROGEN EXCRETION IN THE URINE during rest, expressed as gm. per day. Subjects receiving methyl testosterone during the first part of the experimental period. Averages for two subjects.

Fig. 6. CREATINE, CREATININE AND TOTAL NITROGEN EXCRETION IN THE URINE during rest, expressed as gm. per day. Subjects receiving methyl testosterone during the latter part of the experimental period. Averages for two subjects.

from such medication. The present results indicate that no improvement is obtained with 50 mg. of methyl testosterone daily. However, it is not impossible that somewhat different results would be observed with extremely large dosages, or with physical exercise which placed more emphasis on endurance.

The effect of methyl testosterone on creatine metabolism is of considerable interest. Increased nitrogen storage in dogs given testosterone was observed by Kochakian and Murlin (11). Similar effects in human beings were later reported by a number of workers, notably Kenyon et al. (3) and Albright (16).

It has been assumed that much of the stored nitrogen finds its way to muscle protein, since potassium, phosphorus and water are also stored at the same time. The fact that creatine excretion is reduced under these circumstances in eunuchoids and castrated animals has also led to the belief that the nitrogen storage may be explained in this way.

Williamson and Gulick (5) studied the effect of testosterone propionate injections on the excretion of exogenous creatine by mature male rabbits. Creatine excretion was decreased but the blood level was constant. Paired muscle analyses indicated that, in fact, creatine storage in the muscles did take place so that the reduced excretion might be accounted for in this way. On the other hand the administration of testosterone propionate did not reduce the creatinuria of children (12), nor did it influence the exogenous creatine tolerance of old men (13).

The Jaffe reaction is notably non-specific and we early considered the possibility that the increased 'creatine' in our experiments might actually be some other compound. Attempts to prepare the DuBos enzyme failed owing to death of the bacterial culture. However, it was possible to rule out steroid substances as the active compounds. Aliquots of urines with high creatine titers were extracted with

ether both before and after autoclaving with acid. None of the active material could be extracted with ether in either case.

During the completion of the present work the paper of Wilkins, Fleischmann and Howard (14). appeared. They found that methyl testosterone provoked an exaggerated creatinuria in boys and girls suffering with pituitary deficiency; the creatine analysis was checked by the DuBos enzyme. This report adds weight to our belief that a true creatinuria was produced in our own subjects.

In our subjects there was no significant creatinuria normally. The creatine excretion attendant upon methyl testosterone administration apparently was not due to wasting of muscle because *a*), total nitrogen excretion was not increased, *b*), there was no loss of strength or of the body weight, *c*), there was no change in creatinine excretion such as is seen with muscle wasting in the muscle dystrophies. It would appear that there was an increased production of creatine. Further, by comparison with the other studies cited, it seems that methyl testosterone and testosterone propionate may have different effects on creatine metabolism.

There is no evidence that the creatinuria produced in our subjects by methyl testosterone was due to stimulation of the thyroid gland. McCullagh and Rossmiller (15) have reported that the basal metabolic rate was considerably elevated in patients after continued administration of large doses of this drug. They also found changes in carbohydrate metabolism characteristic of hyperthyroidism. Wilkins, Fleischmann and Howard (14) also found an increased metabolic rate associated with the creatinuria in their treated dwarfs. While we did not determine the metabolic rate of our subjects throughout the experiment, there was no significant difference during the last 3 weeks between the subjects receiving the drug and those receiving placebos. The low normal levels leave no reason to expect that any significant increase had occurred earlier in the experiment. The large excretion of creatine does not seem to be the result of changes in general metabolic rate.

Since creatine metabolism is intimately connected with the carbohydrate cycle in muscle, it is interesting to note that the changes in creatine output were unconnected with any changes in lactate or pyruvate production, or with blood sugar changes during exercise. If muscle phosphocreatine had been significantly changed, current theories would indicate that shifts in rate of phosphate exchange, and therefore of lactate and pyruvate production, would have resulted. Since this did not occur, it would appear that the creatine changes after methyl testosterone are not due to any large shifts within the muscles themselves. The work of Borsook and Dubnoff (17), Baker and Miller (18) and Bodansky et al. (19) would indicate that creatine is largely formed in the liver and kidneys. It would seem, therefore, that a change in creatine metabolism in the liver or kidneys is the most probable effect of methyl testosterone.

SUMMARY

Administration of 50 mg. of methyl testosterone per day to 4 normal young men for periods of 3 and 4 weeks did not significantly change their grip strength nor alter the shifts in water, blood sugar, lactic acid and pyruvic acid produced by a period of short, intense exercise.

No significant changes in basal metabolic rate or in nitrogen output followed the treatment.

Administration of methyl testosterone was associated with a gradual increase of creatine excretion to relatively high levels. The creatinuria gradually decreased after cessation of treatment with the drug. There was an associated small increase in the blood creatine. Creatinine levels in blood and urine were unchanged.

The high creatinuria appeared to be unassociated with any evidence of thyroid stimulation or with any change in the carbohydrate metabolism of the muscles.

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Clinical Reviews in Andrologic Endocrinology: II. Treatment of Androgenic Failure

[A Review Article]

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Segregation of the various etiologic factors in hypogonadism as outlined in the previous paper (1) delineates a rational therapeutic approach and permits a definition of the prognosis. Pertinent information elicited from the history often establishes the existence of testicular failure; *e.g.*, surgical extirpation of both testicles, failure induced by roentgen-ray or radium, persistent non-development or retarded maturation of the sexual system in patients of post-adolescent or adult years and instances, wherein the presumptive diagnosis of testicular failure is ascribable to the metabolic alterations of senescence. The non-existence of gonadal failure is apparent in instances of proven fertility. The ability to fertilize is the most reliable objective evidence of ample testicular function.

In the first paper of this series (1) it was emphasized that two grades of hypogonadism may exist, depending upon the time of onset of testicular failure, *a*), initial preadolescent or adolescent testicular failure, and *b*), adult or intercurrent testicular failure. The therapy of these two types of testicular failure is reviewed.

Therapy of Initial or Adolescent Testicular Failure

Adolescent testicular failure (characterized by varying degrees of genital hypoplasia, delayed puberty, anthropometric discrepancies involving non-union of the epiphyses with resultant overgrowth of the long bones, peculiarities in body habitus ascribable chiefly to abnormalities in fat padding and decreased urinary titers of androgens) may be due to 5 causes: *a*), inanition from dietetic discrepancies, or cachexia from acute and chronic debilitating diseases; *b*), childhood and preadolescent hypothyroidism; *c*), childhood and preadolescent diabetes mellitus; *d*), intrinsic testicular failure; and *e*), childhood and preadolescent hypopituitarism. The diagnosis and treatment of the first three classes of causes is relatively satisfactory. Attention to the diverse extra-endocrine causes of testicular failure, *e.g.*, correction of foci of infection, medical therapeusis of acute and chronic debilitating states, correction of anemia, restoration and stabilization of general body metabolism associated with obesity or leanness, often constitutes effective and rational therapy.

Differentiation between failure due to intrinsic testicular refractivity and that due to inadequate gonadotropic stimulation from the pituitary is somewhat difficult, inasmuch as adequate clinical evaluation of pituitary function is not possible by present diagnostic procedures. Occasionally, the endocrine survey may afford presumptive differentiation. Retardation of somatic growth may suggest pituitary deficiency, whereas statural overgrowth of the long bones, as evidenced by increased measurements of the span over the height and the lower measurement (from the symphysis pubis to the soles of the feet) over the upper measurement (from the symphysis pubis to the top of the head), implies no deficiency of growth hormone (pituitary) but suggests delayed epiphyseal closure ascribable to intrinsic testicular failure.

In the absence of clinical findings permitting these diagnostic departures, therapeutic trials with gonadotropic substances may complete the diagnosis, bearing in mind that the primary purpose of gonadotropic therapy of childhood and adolescent testicular failure is the circumvention of possible subsequent sterility. If the sole reason for gonadotropic therapy is the induction and maintenance of adequate androgenic function of the testes, the more practical, effective and economic therapy is by substituting or supplementing at the testicular level with androgenic preparations.

Hopes of therapeutic success with gonadotropins

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in instances of childhood and adolescent hypogonadism assume that irremediable degenerative alterations in the seminal epithelium and interstitial cells of the testes have not occurred as the result of pituitary deficiency, and that adequate qualitative and quantitative gonadotropic therapy may be administered. Those patients giving desired clinical response to stimulation by gonadotropic therapy may be considered to have had deficient pituitary function, whereas those patients failing to respond to gonadotropic therapy may be assumed to manifest intrinsic testicular refractivity. In that connection, it must be recalled that those patients responding to gonadotropic therapy may effect ultimate gametogenic function whereas those patients requiring substitution therapy with androgenic substances, while anticipating recovery of the endocrine manifestations of the hypogonadal state, will not recover from the underlying seminal inadequacy.

A practical regime of gonadotropic therapy is as follows. *a*), Pretreatment observations which should include those regarding the degree of sexual development with definite measurements of the penis, testes and evaluation of prostatic development; *b*), roentgenologic surveys of osseous growth and epiphyseal development; *c*), serial photographs of the growth responses of the external genitalia; and, if facilities permit, *d*), laboratory data concerning the urinary excretion of androgens and 17-ketosteroids.

The initial trial of therapy is instituted with the chorionic gonadotropin because of its ability to stimulate the interstitial cells of the testes to produce greater quantities of androgenic steroids. Objective clinical observations concerning the response to therapy will be determined by evidences of increased androgen production, *i.e.*, the sexual development will reflect the levels of androgenic function. Having determined by preliminary skin tests that the patient is not allergic to the particular gonadotropic extract selected, intramuscular injections of 250 to 500 international units of one of the commercial preparations of chorionic gonadotropin should be administered daily for a period of 6 weeks. During therapy, weekly observations should note evidences of genital growth and, if possible, there should be studies of the urinary excretion of androgens or 17-ketosteroids which may be increased. If clinical data do not indicate the occurrence of specific testicular response at the end of 6 weeks of intensive therapy, dosages may be doubled and treatment maintained for another 6 weeks.

Patients failing to respond satisfactorily to this trial with gonadotropic therapy should be considered to have intrinsic testicular failure and the advisability of substitutional, androgenic therapy should be evaluated. In that connection, however, it should be recalled that the prognosis for ultimate gametogenic function is poor. On the other hand, adequate androgenic therapy may induce sufficient sexual maturation and consequent development of testicular responsiveness that later trials with gonadotropic therapy may permit adequate functional development of both the endocrine and exocrine components of the testes.

In those patients responding satisfactorily to the initial gonadotropic therapy, treatment should be terminated in order to note the temporary or permanent character of the responses obtained. If sexual regression ensues, two methods of approach are available, *a*), to give repeated courses of chorionic gonadotropin designed to maintain adequate androgenic levels; or *b*), to maintain and promote sexual maturation and development with complemental androgenic therapy. The fact that androgens in maintenance dosages depress spermatogenesis in the adult should not discourage their clinical employment in these circumstances, for no evidence has been submitted that these depressing effects are permanent. Therapy by either of these modes should be continued until the testes are able to function spontaneously or until the need for evaluation of the seminal status becomes apparent. In the latter event, therapy as considered in the third paper of this series should be initiated (2).

Having considered the principles underlying the diagnosis and etiologic differentiation of childhood and adolescent testicular failure, a comprehensive analysis of its therapy may now be presented. From the foregoing discussion, it is apparent that two grades of adolescent testicular failure may exist, *a*), genital hypoplasia associated with statural retardation; and *b*), genital hypoplasia associated with statural overgrowth. The factual data supporting the therapy and prognosis for these two forms may be presented briefly.

GENITAL HYPOPLASIA WITH ACCOMPANYING STATURAL RETARDATION

As indicated above, therapy may be stimulative, (gonadotropic) or substitutional (androgenic) in character, the response to gonadotropic preparations defining the indications for continuation of stimulational therapy.

Gonadotropic Therapy

In the choice of gonadotropic substances one considers *a*), the available commercial preparations of the anterior pituitary gland, the results with which have been generally conceded to be disappointing, and *b*), those preparations obtained from pregnancy urine and pregnant mare serum.

The therapeutic efficacy of growth hormone (anterior pituitary preparation) has yielded conflicting data. Engelbach (3, 4) and his group reported beneficial results from therapy with growth hormone in

7 patients having genital hypoplasia and statural retardation. Moderate improvement in general growth after therapy with growth hormone was observed by Evans, Meyer, Simpson and Reichert (5), Shelton, Cavanaugh and Evans (6), Turner (7) and Lawrence and Harrison (8). Further analysis, however, of the clinical responses to growth hormone by Shelton, Cavanaugh and Evans (9) yielded disappointing results. Our results with growth hormone have not been encouraging.

The majority of the reports of stimulative therapy for hypogenitalism and statural retardation are concerned with the therapeutic efficacy of the chorionic gonadotropin. Sexton (10) reported little success from therapeutic employment of pituitary gonadotropic hormone. Our group likewise has observed no stimulation of growth in 3 patients manifesting genital hypoplasia and statural retardation which were treated with pituitary gonadotropic factor. The observations of Dorff (11–17), Thompson and his group (18–21), Sexton (10), Lichtwitz (22), Schaefer and Kitchen (23), Turner (24) and Mimpriss (25) indicate that therapy of adolescent testicular failure with chorionic gonadotropin results in diverse effects. These are *a*), growth and development of the sexual system as manifested by the appearance of suprapubic hair, enlargement of the penis and scrotum, increased frequency of erections and 'break' in the voice; *b*), increased increment of growth as evidenced by marked spurt in height and osseous development, although evidence that premature epiphyseal closure may result from therapy is lacking; and *c*), redistribution of fat (10) in instances of adiposogenitalism.

Precocious sexual development may result from too enthusiastic or too prolonged therapy with the chorionic gonadotropin, hence it is advisable to note the rate of genital growth periodically during the course of therapy. Discontinuation of therapy prior to adolescence results commonly in partial regression of the genital growth induced by therapy. Unlike therapy with the pregnant mare serum gonadotropin (26, 27), prolonged therapy with chorionic gonadotropin does not evoke antibody formation (11–17, 28, 29) which tends to inhibit testicular activation. Adequate evidence has not been submitted (30) that the chorionic gonadotropin may effect degenerative changes in the testes. Kunstadter (31) has reported definite genital growth and sexual maturation in a group of 14 boys treated with 10 to 20 Cartland-Nelson units of equine gonadotropin 3 times weekly for several weeks.

Considerable difference of opinion exists concerning the optimum time for institution of gonadotropic therapy in instances of adolescent testicular failure, especially in those cases thought to be adiposogenitalism. Dorff (11–17) believes that therapy should be initiated not earlier than 5 years and not later than 13 years. On the other hand, considerable evidence has been submitted by Ellis and Tallerman (32), Gray (33), Bruch (34) and Werner (35) that many instances of genital hypoplasia ascribable to adiposogenitalism will progress normally to puberty without therapy other than dietary restriction. Werner (35) believes gonadotropic therapy designed to effect the sexual and statural alterations of puberty should not be considered prior to 16 years of age, except in those instances wherein severe psychological difficulty results from genital and statural underdevelopment.

Androgenic Therapy

Substitutional therapy with available commercial preparations of androgenic substances is indicated in those instances of genital hypoplasia and statural retardation which fail to respond to stimulative therapy with gonadotropic perparations. Many data have accrued concerning the efficacy of androgenic therapy in hypogonadism, the criterion of production of genital growth being accepted generally, whereas the responses of somatic growth to androgenic therapy are regarded not without equivocation. Diverse routes of administration of androgenic substances have been employed: *a*), intramuscular, *b*), oral, *c*), percutaneous and *d*), implantation of crystalline pellets. Most of the reports predicate the employment of androgenic preparations in adolescent testicular failure upon one or more of the following results obtained: *a*) development and maturation of the sexual system; *b*), production of somatic growth; and *c*), an undetermined rôle of psychological stabilization and metabolic alterations resulting in increased vigor and activity and aggressiveness.

As stated above, therapy with androgenic preparations may include intramuscular administration of testosterone propionate, oral therapy with methyl testosterone or testosterone propionate (accepted generally as being ineffective by mouth), inunction with ointments containing testosterone propionate in a lanolin-petrolatum base, and implantation of pellets of crystalline testosterone or methyl testosterone. Selection of the therapeutic regime is determined by the availability of the products, estimation of the need for prolonged therapy and the cost. Exhaustive reviews of androgenic principles have been submitted by Koch (36–39), Vest and Howard (40), Moore (41) and Hamilton (42).

Production of genital growth. Clinical reports attesting the induction of genital growth following intramuscular therapy with testosterone propionate have been reported by Kenyon and his group (43–47), Hamilton (42, 48), McCullagh and his coworkers (49–53), Foss (54), Moricard and Bize (55), Vest and Howard (40, 56), Riches (57), Walther and Willough-

by (58), Nathanson and Towne (59), Ketcham (60), Turner (61), Kearns (62), Dunn (63). Moehlig (64), Aub (65) and others. Dependent upon the severity of the testicular failure, the dosages of testosterone propionate usually employed are 25 mg. 3 times weekly, or more often, until the desired genital growth has resulted; thereafter the dosage is reduced to maintenance levels of 10 mg. 3 times weekly or more often.

The intramuscular administration of testosterone propionate to the hypogonadal male effects characteristic responses (41, 42, 49–53, 59) which may be considered briefly.

a) Alterations in the blood volume and pigmentation of the skin (66, 67) occur within an hour following injection. Simultaneous with the increase in blood volume (occurring generally throughout the body, except in the buttock) and of the percentage of hemoglobin, there is an increase, although to a lesser degree, of melanin and related substances. As a result, the pallor and waxy appearance of the skin of the hypogonadal individual is replaced by flushing and deepening of color.

b) Appearance of spontaneous erections and increase in the erectile power may ensue within several hours.

c) Increased excretion of urinary androgens (49–53, 59, 68–74) occurs within a few hours following injection of testosterone propionate with a slow return to normal levels within 48 hours, although the androgen excretion may be increased for several days. These increases may be related to increased excretion of androsterone, a product of testosterone metabolism, although the recovery of the active substance varies from 14 to 70 per cent, the fate of the remainder being unknown. Clinical data (49–53, 68–71) suggest that maintenance of the level of urinary androgens within the range of normal is evidence that ample testosterone has been administered to effect the desired clinical responses.

d) The appearance of the secondary sexual hair follows within a few weeks, axillary and pubic hair being the first to grow. The beard, too, becomes stiffer and coarser. After several weeks of therapy, hair appears on the trunk and limbs. Increased oiliness of the skin may result and the appearance of acneiform responses may ensue.

e) Genital enlargement and development occurs likewise within a few weeks. The penis undergoes considerable growth, the scrotum manifests proportionately less growth and development of the prostate is perceptibly slower. Nocturnal emissions may be experienced and the quantity of the semen is considerably increased. Inadequate clinical evidence exists to support the assumption that testicular growth may be stimulated by androgenic therapy, although Webster (75) reported testicular growth in 3 hypogonadal boys treated with androgens.

f) Deepening of the voice is a characteristic alteration ascribable to androgenic therapy. This may be related to congestion and roughening of the mucous membrane of the larynx (42) or to alterations in growth of the tracheal or laryngeal cartilages.

g) Increased body weight and diverse metabolic alterations may be induced by androgenic therapy. The studies of Kenyon and his group (43–47) have suggested that the gain in weight may be ascribable to retention of water, electrolytes and nitrogen resulting from androgenic therapy, a finding comparable to similar phenomena produced by adrenal cortical substances (76–81) except for the fact that hypogonadal males treated with testosterone propionate manifest diminished urinary potassium excretion (43–47) whereas patients with cortical adrenal failure treated with adrenal steroids show increased urinary potassium excretion. The various metabolic alterations (43–47) in the hypogonadal male treated with testosterone propionate may be summarized as: a reduction in the volume of urine; retention of 1 to 4.5 gm. of nitrogen daily as reflected by uniform decline in urinary nitrogen in the form of urea, the urinary creatinine being unaffected (42, 43–47); no alterations in the nitrogenous components of the blood; retention of 0.33 to 0.55 gm. of sodium and a proportional retention of associated chloride ascribable to decline in urinary sodium and chloride excretion (42, 43–47); slight decline in urinary sodium and chloride excretion; slight decline in urinary potassium excretion; considerable reduction in urinary inorganic phosphorus excretion; no significant alterations in serum lipoid values (82); minimal or no alteration in the basal metabolic rate, the fasting respiratory quotient, pulse rate and blood pressure. The retention of nitrogen and proteins throughout the body generally permits explanation of the unusual somatic growth accompanying precocious adolescence, *i.e.*, androgenic therapy designed to stimulate genital growth may effect diverse somatotropic influences (43–47).

h) Alterations of osseous development, *i.e.*, premature or advanced epiphyseal closure, have been related to androgenic therapy both by animal experiments (83, 84) and by clinical observations of Howard and Vest (56) and McCullagh and McGurl (85). The question remains equivocal, however, inasmuch as other studies (75, 86–90) have not confirmed this observation.

i) Nelson (91, 92) has observed favorable alterations of cardiac output in hypogonadal males treated with androgenic preparations.

Therapy of hypogonadal males with androgenic substances has resulted in various complications. *a*) Edema of the lower extremities, especially the ankles, has resulted from over-enthusiastic therapy with testosterone propionate (93). *b*) Bilateral gynecomastia has resulted from therapy with either testosterone propionate or methyl testosterone (94), suggesting, therefore, that these androgens may exert specific stimulating effects upon breast tissue. *c*) Annoying frequency of erections, which may result in priapism unrelieved by intercourse (54) has been observed. Reduction in dosage of testosterone propionate usually effects relief. *d*) Excessive genital growth may be induced by prolonged therapy (95, 96) in instances of adolescent testicular failure, the precocious development and other evidences of maturity defining the need for cautious therapy of young boys with androgenic preparations. On the other hand, Ehrenstein (97) and Kunstadter (95) warn that possible gonadal

damage may follow androgenic therapy. *e*) The question of possible premature epiphyseal closure secondary to androgenic therapy has been discussed. *f*) The production of acneiform responses (49–53) by androgenic therapy constitutes an annoying complication. g) The studies of Moore (98), Heckel (99) and McCullagh and McGurl (49–53) have demonstrated that spermatogenic function is impaired by androgenic therapy, although Rubinstein and Kurland (100) report increased spermatogenesis with small dosages of 5 mg. of testosterone propionate 3 times weekly.

Due, perhaps, to inactivation by the liver (101, 102), the oral administration of testosterone propionate has proven ineffective clinically (68–71). Based on the animal experiments of Miescher and Tschopp (103) and Emmens and Parkes (104), Foss (54, 105–108) employed methyl testosterone orally in the therapy of hypogonadal males and obtained evidence of favorable androgenic responses. These observations have been confirmed by Loeser (109, 110), McCullagh (111), Dorfman and Hamilton (68–71), Kearns (112), Tager and Shelton (113) and Byron and Katzen (94). The maximum oral dosage has been accepted generally to be 100 mg. daily, which is taken commonly as 4 divided doses when the stomach is empty. The medication is followed by one-half glass of warm water to insure maximum absorption. In that connection, the administration of bile acids by mouth is said to enhance considerably the oral effectiveness of androgenic substances (114–119). The maintenance dosage of methyl testosterone is considered to be 50 mg. daily, denoting, therefore, a dosage requirement 4 to 6 times greater than that of intramuscular testosterone propionate. Minimal toxicity to methyl testosterone orally has been experienced in the form of slight nausea, anorexia and gastric irritation which is relieved by alkaline mixtures. A possible explanation for the oral effectiveness of methyl testosterone as compared to testosterone propionate has been advanced by Biskind (101). His experiments suggest that methyl testosterone is absorbed from the gastrointestinal tract through the lacteals and lymphatics rather than the portal circulation, avoiding, thereby, immediate inactivation by the liver. The results following administration of methyl testosterone orally differ from those following intramuscular testosterone propionate in three ways. *a*) Clinically effective doses of methyl testosterone produce no increase in urinary androgenic excretion (68–71, 111) whereas pronounced increases follow therapy with testosterone propionate. *b*) Prolonged therapy with methyl testosterone orally requires gradual increases in dosage to maintain clinically effective levels (94, 111). McCullagh (111) suggests that this may be related to an increased ability of the liver to metabolize methyl testosterone. *c*) Slight elevation of the basal metabolic rate has been observed (94, 111) following therapy with methyl testosterone whereas little or no alteration in the basal metabolic level is induced by therapy with intramuscular testosterone propionate (43–47). The chief objection to clinical employment of methyl testosterone is the cost of the preparation.

The effectiveness of the percutaneous employment of testosterone propionate in the therapy of diverse grades of hypogonadism has been demonstrated by Moore, Lamar and Beck (120), Foss (105–108), Kearns (62) and Tager and Shelton (113). An effective daily dosage may be considered to be 14 mg. of active principle (113) in 7 gm. of petrolatum-lanolin base, although Foss (105–108) observed that the dosage of testosterone propionate by inunction is two or three times the effective intramuscular dosage.

In instances wherein prolonged and uniform therapy with androgenic preparations is desirable, the advisability of intramuscular implantation of pellets of crystalline androgenic substances may be considered. Favorable responses in the therapy of hypogonadal males with implantations of pellets of pure testosterone have been observed by Deanesly and Parkes (121, 122), Howard and Vest (56), Vest and Howard (123), Hamilton and Dorfman (124), Foss (105–108) Eidelsberg and Ornstein (125) and Biskind and his group (126–128). Hamilton (42) recommends intramuscular implantation of 960 mg. of testosterone divided between 4 pellets, each of which is 5 mm. in diameter and 7 mm. in length. Biskind and his coworkers (126–128) prefer methyl testosterone rather than testosterone, inasmuch as the high melting point of methyl testosterone permits sterilization of the pellets in the pressure autoclave whereas the pellets of testosterone are considerably more difficult to sterilize. They estimate the effective clinical dosage of methyl testosterone to vary from 2 to 3 mg. daily, indicating, therefore, that approximately one-fifth of the daily maintenance dosage of injected testosterone propionate is required by the implantation method.

Inasmuch as therapy of hypogonadal states with androgenic preparations is substitutional in character, therapy must be continued at maintenance levels sufficient to effect the desired clinical responses. Eidelsberg and Ornstein (125) observed no ill effects with prolonged androgenic therapy other than too frequent erections and increased libido. Withdrawal of therapy effects diverse alterations (49–53) such as prompt diminution in libido and erectile power, pronounced reduction in the volume of the seminal fluid ascribable to decreased prostatic and vesicular secretion, atrophy of prostate and seminal vesicles, minimal or no regression of the external genitalia, and

no alterations in the distribution of sexual hair, skeletal maturation and laryngeal growth.

Therapy of adolescent testicular failure oftentimes may be discontinued when clinical responses denote the development or recovery of testicular function. This may be judged by *a*), development and maturation of the sexual system; *b*) recovery from diverse extra-endocrine factors attributable to testicular failure; *c*), rational therapy of various endocrinopathies such as hypothyroidism and diabetes mellitus; *d*) surgical and medical therapeusis of various urologic diseases; *e*), an induction of adequate genital growth by androgenic therapy so as to permit response to gonadotropic therapy and *f*), sufficient modification of skeletal growth by androgenic therapy so that indications for further treatment are nonexistent.

Alterations of somatic growth. Although the clinical observations of Howard and Vest (56) and McCullagh and McGurl (85) suggest that prolonged therapy with androgenic principles may permit advanced epiphyseal closure, reports concerning the stimulation and production of statural growth by androgenic therapy have been submitted by Webster (75, 87, 88) Villaret, Justin-Besancon and Rubens-Duval (86), Moricard and Bize (89) and Rapfogel (90). Webster (75, 87, 88) administered intramuscularly 75 to 125 mg. of testosterone propionate weekly to 8 hypogonadal boys ranging in age from 9 to 18 years, observing an increase in the rate of growth from 1.36 centimeters per 100 days during the control period to 3.6 centimeters per 100 days during the treatment period. Upon discontinuation of therapy, the average growth rate decreased to 1.56 centimeters per 100 days. Webster (75, 87, 88) has stated that the mechanism of the growth spurt following androgenic therapy is obscure, although it may be related to indirect alterations mediated via the pituitary. Kenyon (43–47) suggests that the retention of nitrogen and proteins generally throughout the body may be related to diverse somatotropic influences of androgenic substances.

Our group, likewise, has observed stimulation of statural growth induced by therapy with testosterone propionate in 5 patients ranging in age from 15.5 to 19 years. Three patients received 10 mg. doses of testosterone propionate thrice weekly, the growth responses during therapy being 1.38 inches in 193 days, 1.5 inches in 64 days and 2.0 inches in 151 days, respectively. Although the bone age of all 3 patients was retarded 2 or 3 years, no advancement of bone age occurred during therapy. The remaining 2 patients were treated with 25-mg. doses of testosterone propionate thrice weekly, the growth responses being 1.25 inches in 2 months and 1.5 inches in 11 months, respectively. Epiphyseal closure, however, was markedly accelerated by doses of 25 mg. of testosterone propionate thrice weekly, the bone age apparently being advanced 4 years in one patient treated for 11 months and 2 years in the other patient, treated for two months.

Stabilization of psychological reactivity. In instances of adolescent testicular failure wherein persistence of genital hypoplasia or altered statural growth induce diverse alterations of psychological responsiveness, therapy of the hypogonadal state, either of a stimulative or substitutional character, is advised (42). This does not suggest, however, the inference that alterations in testicular function are related directly to the psychological constitution of the individual.

GENITAL HYPOPLASIA ASSOCIATED WITH STATURAL OVERGROWTH

The development of testicular failure during the preadolescent epoch, *i.e.*, prior to the closure of the epiphyses of the long bones, results oftentimes in marked overgrowth of the long bones, as evidenced by increase of the lower measurement (from the symphysis pubis to the bottom of the feet) over the upper measurement (from the symphysis pubis to the top of the head) and increased measurement of the span over the height. In the choice of a rational therapy with androgenic principles one should consider not only the correction of the genital hypoplasia but the curbing of the osseous growth (56, 83–85) to prevent the cosmetic inelegance. That epiphyseal closure, perhaps, may be induced by therapy with doses of 25 mg. of testosterone propionate thrice weekly has been indicated above.

THERAPY OF ADULT OR INTERCURRENT TESTICULAR FAILURE

Intercurrent androgenic and seminal failure of the adult produce regressive alterations in the sexual system with little or no change in skeletal growth. The clinical observations denoting adult testicular failure include *a*), evidences of testicular atrophy or decrease in testicular firmness; *b*), marked depression of seminal values; *c*), decrease in the size of the prostate and seminal vesicles; *d*), decreased *libido sexualis*; and *e*), androgenic values of urine which may be lower than normal, but which frequently are normal or even higher than normal. The etiologic factors underlying adult testicular failure are identical with those attributed to adolescent testicular failure: *a*), extra-endocrine factors, such as inanition and cachectic states resulting from acute and chronic diseases; *b*), adult hypothyroidism; *c*), adult diabetes mellitus; *d*), intrinsic testicular inadequacy; and *e*), adult hypopituitarism. The diagnosis and treatment of the first three classes of causes, *i.e.*, the extra-endocrine

factors, thyroid deficiency states and diabetes mellitus, is relatively satisfactory. The differentiation of the last two classes, *i.e.*, adult testicular failure due to intrinsic testicular non-responsiveness or to inadequate stimulation by the pituitary, if not permitted by the history and the endocrine survey, may require consideration of receptivity of the gonads to stimulative (gonadotropic) therapy as outlined in the following paragraphs.

Clinically, most cases of intercurrent androgenic and seminal failure of the adult are ascribable to causes intrinsic to the testes and are not associated, therefore, with hypogonadotropic functions of the pituitary. Moreover, it is unlikely that the most potent gonadotropins are capable of re-instituting normal function in testes subjected to diverse forms of destruction. Our experience with intensive therapeutic schedules of chorionic gonadotropin, alone or in combination with one another, or with testosterone propionate, in the therapy of seminal inadequacy has been disappointing. If gonadotropic therapy of germinal failure proves unsatisfactory, therapy of the androgenic deficiency states by substitution at the testicular level with androgenic steroids is the treatment of choice, providing, of course, that indications exist for androgenic therapy.

If a therapeutic trial of gonadotropins seems indicated under these circumstances, a suggested schedule of treatment is as follows: Pretreatment observations include careful evulations of the seminal fluid (with reference to volume, number of spermatozoa per cc. of fluid, motility, percentage of abnormal forms and estimations of viability) secured after periods of established continence (*i.e.*, after 7 days) and, if facilities permit, determination of the values for urinary androgens. Having determined the non-existence of possible allergy by preliminary skin-testing, dosages of 500 international units of one of the commercial preparations of chorionic gonadotropin are injected daily for a period of 6 weeks. During the last week of therapy or at its immediate termination, estimation of the therapeutic results is determined by repeated seminal studies, alterations in the prostate, seminal vesicles and consistency of the testes and androgenic values of the urine. If the testes respond to this form of therapy, increases in androgenic urinary titers should be noted, although significant alterations of seminal values will not be anticipated with the exception of those alterations which are affected by improved androgenic function. The rationale of this form of therapy is to stimulate if possible an increased production of androgens and affect, thereby, androgenic 'priming' of the male genital system before therapeutic attempts to stimulate spermatogenesis are initiated.

Both androgenic and germinal failure exist in these patients and no clinically effective pituitary gonadotropin is available, so that in attempted therapeutic stimulation of spermatogenesis one should probably employ both chorionic and equine gonadotropin; the use of a preparation of 'pituitary synergist' and chorionic gonadotropin[1] also may permit satisfactory therapy in these cases. As in the preceding therapeutic schedule, pretreatment observations include seminal studies and androgenic determinations. (Those determined at the conclusion of the initial therapy with chorionic gonadotropin are satisfactory.) Immediately following the 6 weeks of therapy with chorionic gonadotropin previously described, combined gonadotropic therapy is instituted according to the following schedule: When preliminary skin-testing with each gonadotropic preparation is completed, dosages of 500 international units each of chorionic gonadotropin and equine gonadotropin or of 30 'synergy' units of the preparation of pituitary synergist and chorionic gonadotropin are injected intramuscularly daily for a period of 4 to 6 weeks. At the conclusion of this therapeutic schedule, evaluation of the treatment is determined by repeated seminal studies and determination of the androgenic values will indicate the occurrence or non-occurrence of specific responses. Further similar studies should be made 4 to 6 weeks following discontinuation of therapy in order that delayed responses may not be overlooked.

In those patients failing to respond to this form of treatment it is doubtful that further gonadotropic therapy will prove satisfactory. On the other hand, additional series of therapy as outlined above with adequate rest periods may be given to those patients effecting satisfactory responses.

Having considered, therefore, the principles underlying the diagnosis of the etiology of the adult testicular failure, it will be noted that the therapy for androgenic and seminal deficiency in the adult embraces commonly three chief purposes: *a*), initiation or restoration of gametogenic responses compatible with the fertile state; *b*) prevention of regressive alterations in the sexual system which may diminish the *potentia coeundi* of the hypogonadal male or effect diverse psychological maladjustments; and *c*), therapy of metabolic alterations resulting in diminished energy production by the hypogonadal individual.

It is apparent that the circumvention of existing sterility is the paramount indication for therapy of adult testicular failure. The correction of seminal failure is permitted only by the development of intrinsic testicular receptivity to gonadotropic stimulation. In instances wherein gonadotropic therapy is ineffective and recourse to substitutional therapy,

[1] One such preparation is prepared by Parke, Davis and Company, Detroit, Mich. (Synapoidin).

according to the schedules described above, is indicated, recovery of the seminal function, *i.e.*, fertility, cannot be anticipated. Oftentimes, however, androgenic therapy may maintain the sexual system in a state of receptivity while local pathologic processes are subjected to indicated therapies, recovery from the intrinsic testicular failure permitting the return of responsiveness to gonadotropic activation.

The relationship of diverse grades of adult testicular failure, as manifested by varying degrees of regression of the sexual system, to psychological instability remains unsettled. Miller, Hubert and Hamilton (129), Dunn (63), Werner (130), Sharpey-Schaefer (131), Thomas and Hill (132) and Daniels and Tauber (133) have observed improved psychological adjustment in hypogonadal males following androgenic therapy. These studies, however, do not permit correlation with the physiologic epoch of testicular failure, *i.e.*, the preadolescent period, wherein psychological alterations attributable to androgenic deficiency are non-existent. Furthermore, the various psychologic maladjustments of hypogonadal males cannot be segregated from latent imbalance of the autonomic nervous system aggravated by alterations in neuro-endocrine sympathies.

The studies of Lipross (134), Papanicolaou and Falk (135), Hesser, Longworthy and Vest (136), and Simonson, Kearns and Enzer (137) suggest relationship between muscular development and performance and intrinsic androgenic levels. Further observations concerning the mechanism of increased energy production induced in hypogonadal males by androgenic therapy are indicated before pertinent conclusions may be formulated.

SUMMARY

1. The ultimate aim of therapy of testicular failure is development of or restoration of fertility.

2. Rational therapy of testicular failure is determined by the diagnosis of and the degree of testicular impairment and differentiation of the etiologic factors contributing to testicular failure.

3. The various causes of testicular failure have been classified and the mechanism of their impairment of testicular function has been discussed.

4. The cause of testicular failure determines the prognosis relative to physiologic recovery and defines the therapeutic approach.

5. Diagnostic procedures to determine testicular responsiveness to gonadotropic therapy permit differentiation of testicular failure ascribable to intrinsic refractivity of the testes and defines the conditions for androgenic therapy. The procedures and interpretation of these therapeutic tests have been considered.

6. The limitations and procedures of various therapeutic measures available at present for therapy of testicular failure have been discussed.

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COMMUNICATIONS TO THE EDITORS

Vasomotor Effects of Progesterone

Several years ago during an investigation[1] of the urinary excretion of sodium pregnanediol glucuronide following intramuscular injection of progesterone in sesame oil into volunteer members of a group of males, one of us (D. V. H.), experienced some subjective symptoms which were related theoretically to vasomotor effects of this hormone. In view of the fact that experimental studies upon laboratory animals have indicated that progesterone may influence the vasomotor system, and despite the fact that our clinical observations concern only one individual, it seemed advisable to report these findings.

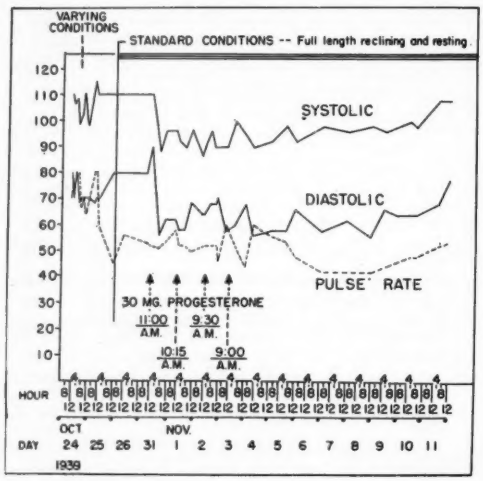

Fig. 1. Daily recordings of blood pressure and pulse rate of one of us (D. V. H.) before, during and following the intramuscular administration of progesterone in oil, 30 mg. daily for four days.

During the course of daily intramuscular injections of 30 mg. of progesterone in sesame oil* (10 mg. to 1 cc. of oil) for 4 days, *D. V. H.* experienced a sudden onset of an acute depression, with psychomotor retardation and associated feelings of impending calamity. These symptoms lasted throughout the 4-day period of treatment and for about 2 days thereafter. The experience was unique and it was judged to be associated too closely with the progesterone therapy to be entirely incidental. That these symptoms were not without foundation was apparent from a concomitant fall in pulse rate and blood pressure. Resting pulse rates were recorded which were as low as 42 per minute while the blood pressure fell to 84 mm. Hg systolic, and 44, diastolic. These values were far below the individual's normal levels.

Some weeks later, the experiment was repeated after a record of the normal blood pressure and pulse rate had been made. The vasomotor effects of progesterone are presented in figure 1. The blood pressure fell dramatically and did not return to normal levels for 12 days. Intramuscular injections of similar amounts of sesame oil without progesterone, however, produced similar vasomotor changes. This fact has been observed also in experimental animals,[2] but there were enough differences between the results following injections of the oil and these following injections of oil and progesterone to indicate a possible specific vasomotor effect of progesterone.

Our plans to extend these clinical studies and to investigate in experimental animals the effects of progesterone given intramuscularly in non-vegetable oil vehicle (propylene glycol) were interrupted. Subsequently, however, it has been shown[3] that the intraperitoneal administration of progesterone to rats in dosages varying from 17 to 22 mg. resulted in appreciable decreases in systemic blood pressure. On the other hand, it has been reported that the intravenous administration of α-estradiol to dogs failed to effect any significant alterations in blood pressure.[4]

This personal observation by us suggests that clinical studies of vasomotor responses of males and females following implantation of crystals or pellets of progesterone might yield interesting and significant data upon this supposed effect of progesterone.

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* Proluton and sesame oil supplied by Schering Corporation, Bloomfield, N. J.

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Androgenic Therapy in Women

To the Editor:

In a recent letter to the Editor[1] Dr. E. C. Hamblen sharply condemns the use of androgens in the practice of gynecology. He bases his discussion upon a particular case that came to his attention, one in which a total of 2500 mg. of testosterone propionate was administered by some physician over a period of 10 months to a girl of but 15 years of age. This was truly an astonishing procedure.

One point which is fundamental and with which none will take issue is that the excessive use of any pharmacologic agent, hormonal or otherwise, is harmful. It must be admitted that following large parenteral doses (500 to 600 mg. per month) of testosterone propionate, undesirable side-reactions such as temporary virilization may develop. Such dosage used parenterally has given cause for protestation that androgens are 'contrasexual.' But it well may be that it is the dosage and not the hormone that is contraphysiologic. The administration of such massive doses as 2500 mg. of testosterone propionate to a 15-year-old girl or of 500 to 600 mg. per month to adults is contrary to good judgment or experience. These are very massive doses and in themselves do not constitute *a priori* arguments against the use of pharmacologically effective doses of androgens in gynecologic therapy. One can not logically argue against the use of any agent from the results of its abuse.

Are androgens contrasexual? Androgens presumably must play some rôle in the physiologic economy of the female, otherwise how can we account for the appearance of the same two androgens in the urine of normal women as have been identified in the urine of normal males (the Callows; Womack and Koch)? Likewise, estrogens are found in the urine of males; in fact, paradoxical as it may seem, an excellent source of certain estrogens is the urine of the stallion.

Is there a hypo-androgenic state in the female? Doctor Hamblen perhaps rightly questions the existence of a hypo-androgenic state which will justify the use of androgenic therapy in the female. However, his assumption that that might be the reason for its use by clinicians is entirely gratuitous. Epinephrine is useful in asthma in spite of the fact that a deficit of epinephrine has never been proven to exist in asthmatic patients. The use of androgens, therefore, does not imply an androgen deficit or hypo-androgenic state, but rather that its use at times is expedient.

Are androgens ovary negating? The voices that have been raised against the use of androgens in the female arise from the concept that gonadal hormones should be sex-specific and the observation that defeminizing and ovarian negating effects are produced by androgens following massive parenteral dosage. The parenteral use of massive doses of testosterone propionate in the female is contraphysiologic and ovary-negating. The use of comparatively large dosages of estrogens is also ovary-negating. The ovary-negating effects which may be obtained with estrogens or androgens are mediated through the hypophysis by inhibition of the follicle-stimulating hormone. Pharmacologically effective doses of testosterone propionate, which are far below the virilizing level, have been employed in several hundred cases by our group; therapeutic effectiveness has been the result in a goodly number of cases. When such dosage proved therapeutically ineffective the administration of the hormone was discontinued rather than increased. In more than 100 patients pellets were introduced in doses of 25 to 400 mg. and in not one single instance was masculinization induced. It is true that Loeser[2] observed transitory signs of masculinization in every one of 8 patients in his series. However, he used dosages of 600 to 1650 mg. An evaluation of our results indicated that pellet implants of testosterone propionate in doses as large as 400 mg. were capable of alleviating many aberrations of gynecic function without any indication of suppression of hypophyseal-gonadotropic function or interference (antagonism) with the action of endogenous estrogen or progesterone on the uterus and vaginal mucosa. Ovulation, periodic follicle maturation, and glycogen desposition in both secretory endometrium and vaginal mucosa was not interfered with in cyclically functioning women. Furthermore, in menometrorrhagia, the therapeutic results could not be ascribed definitely to the influence on the hypophysis or ovary, since the endometrial pattern, which reflects hypophyseal-gonadal relationship, was frequently maintained in the status it had attained before pellet implantation. Excessive bleeding was arrested in several cases in spite of persistence, for instance, of the condition of cystic glandular hyperplasia. It is apparent, therefore, that androgens possess certain pharmacologic properties which permit of its effective use in dosages which do not suppress ovarian activity.

It is true that androgens are frequently employed in conditions in which estrogens may yield equally good or better results. There cannot be any doubt, however, that androgens have a place in the therapeutic armamentarium of many gynecic disturbances. The following instances are a few examples.

1. The menopausal patient *a*) whose hot flashes are relieved by estrogen therapy but who is disturbed by the accompanying uterine bleeding; the simultaneous administration of small doses of testosterone propionate will prevent uterine bleeding in the greater number of cases; *b*) in whom estrogens produce marked nervous tension states, uterine bleeding, breast pain, abdominal bloating and pelvic discomfort. Androgens frequently yield gratifying results without undesirable side-reactions.

2. In cases of cyclomastopathy in which estrogen or progesterone fail to alleviate the painful and nodular breasts, testosterone propionate therapy in doses of 10 to 25 mg. at weekly intervals for several months frequently yields excellent results. In some of these cases estrogens aggravate the condition. Furthermore, in the suppression of lactation, androgens are superior to estrogens—the former suppress, the latter limit lactation.

3. In cases of dysmenorrhea in which some degree

of endometriosis is suspected or in which small intramural fibromyomas may be present, androgen therapy will yield results whereas estrogen therapy is contraindicated.

4. Androgens may be used for the woman approaching the menopause who has excessive bleeding associated with small fibromyomas or for the woman with large fibromyomas in whom surgery is contraindicated or not feasible.

5. The disturbing syndrome of nocturnal frequency of urination when no evident pathologic basis exists for it, may be alleviated by testosterone propionate and the results cannot be matched by estrogen administration.

6. At times, because of acquired frigidity on the part of the female, it may be necessary, if for none other than personal reasons, to restore sexual libido in the hope that dissolution of a marital union may be prevented. Testosterone propionate will restore libido in women who once have known libido but have lost it. In this particular type of case androgens are specific.

There are many pharmacologic properties peculiar to testosterone which other steroids do not possess. Gonadal steroids must be thought of not only in terms of sex-specificity, but also in terms of chemical substances which profoundly influence electrolyte balance, carbohydrate metabolism and nitrogen storage. In this respect testosterone propionate has been shown to be capable of restoring and maintaining a positive nitrogen balance (Albright). The beneficial action to the body economy which may accrue from androgen administration in such patients (with negative nitrogen balance) eliminates the consideration, whether one is dealing with a male or female.

Finally, it should be stressed that clinically effective results are obtainable with dosages of androgens which do not exceed 200 mg. per month, during periods of treatment which are not unduly prolonged without intervals of freedom from therapy. When androgens are so employed, the clinician need not fear the development of arrhenomimetic phenomena. However, I should like to state that I am in complete accord with Doctor Hamblen's emphasis as to the possible irreversible masculinizing symptoms that may result from the injudicious administration of androgens.

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Abstracts of
CURRENT CLINICAL LITERATURE

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ADRENAL

CAHILL, G. F., M. M. MELICOW AND H. H. DARBY.

Adrenal cortical tumors. Types of nonhormonal and hormonal tumors. *Surg. Gynec. & Obst.* 74: 281. 1942.

Adrenal cortical tumors may occur with or without hormonal syndromes. Of those occurring with hormonal syndromes, changes may be due to excessive formation of androgens or of estrogens or of other steroid substances not yet identified. Symptoms vary according to the type and amount of hormone or hormones produced and by the age and sex of the patient. Adrenal tumors are readily visualized by X-ray after perirenal air insufflation. Removal of adrenal tumors by the transperitoneal route is surgically best. Acute adrenal deficiency occurs only, or mostly, in those with symptoms described as Cushing's syndrome. Therapy is similar to that of acute Addison's disease. Histologically tumors producing hormonal syndromes have cytoplastic lipoid vacuoles in amounts proportional to the symptoms.—*D. A. M.*

HELLWIG, C. A. AND L. H. FORMAN.

Pellagra and internal secretion. *Am. J. Clin. Path* 12: 210. 1942.

Report of a case of pellagra associated with severe endocrine symptoms is presented. The autopsy showed a marked atrophy of the cortex of the adrenal gland with lipoid depletion, atrophy of the pituitary, resting thyroid, and hyperplasia of the Langerhans islands of the pancreas. The clinical and anatomical findings suggest a relationship between the pellagra-preventing vitamin and the hormones, especially the one of the adrenal cortex.—*E. von H.*

ENDOCRINE GENERAL

BREA, LUIS MARIA.

Hormone therapy in prostatic adenoma. *Rev. sudamericana endocrinol.* 24: 495. 1941.

Treatment consisted of daily injections of 5 to 10 mg. of testosterone propionate for 5 days followed by 5 mg. twice weekly. The total amount given was over 50 mg. 19 cases are reported. Frequency of urination was diminished in the majority of the cases, dysuria showed improvement in 50%, retention was improved in six cases. While the adenoma itself did not reveal changes in any case the general feeling of well-being was the most conspicuous consequence of the treatment.—*A. E. M.*

FREYBERG, R. H.

Treatment of arthritis with vitamin and endocrine preparations. *J.A.M.A.* 119, 1165. 1942.

Desiccated thyroid was of limited value in selected cases. Parathyroid and anterior pituitary was of no value. Estrogens were of value in the fibrositis of hypomenorrhea but not in spondylitis rhizomelica. Endocrine preparations are only of value in rheumatic disease when a definite hypofunction of an endocrine gland is present.—*C.C.P.*

MACDONALD, I.

Mammary carcinoma: a review of 2636 cases. *Surg., Gynec. and Obst.* 74: 75, 1942.

A statistical review of clinical records from Cancer Archives of the American College of Surgeons have revealed the following factors: Age of the patient seems not to have any constant prognostic significance although best therapeutic results are obtained in the 35–50 year age group, the least favorable in the sixth decade. A history of familial cancer occurred in 20% of the patients, there being in the cancerous relatives an excess of breast cancer 3 times greater than in the general population. Nulliparae are slightly more prone to develop carcinoma than multiparae, the number of children borne having no relationship to prognosis. A high incidence of failure of lactation in parous women is found in those developing breast carcinoma. 40% of attainable five year cures may be lost by failing to employ radical treatment in Stage II cases. Ten year follow-ups are necessary for true evaluation of therapeutic measures.—*Author's summary.*

GONADS

ALBERT, S. AND H. SELYE.

The effect of various pharmacological agents on the morphogenetic actions of estradiol. *J. Pharmacol. & Exper. Therap.* 75, 308. 1942.

The synergisms and antagonisms of the steroid hormones may help the clinican to accentuate desired therapeutic effects or diminish harmful side effects. Using estradiol in a fixed dose the modifying effect of steroids was studied. They found: 1. Androstenediol was most potent in preventing the loss of body weight due to estradiol. 2.

Testosterone and methyl testosterone gave the most clear-cut inhibition of hypophysis hypertrophy. 3. Thymus involution is accentuated by all of the steroids. 4. The decrease in testis and kidney weight is prevented only by highly active androgen.—C.C.P.

DANZIGER, L.

Estrogen therapy of agitated depressions associated with the menopause. *Arch. Neurol. and Psychiat.* 47: 305. 1942.

Of 164 cases of probable involutional melancholia previously reported in the literature and treated with estrogens, 79, or 48%, recovered or improved markedly. Of 29 apparently similar cases treated with placebos, 2, or 7%, recovered or improved markedly. Statistical analysis indicates the results in the two groups are significantly different. Seven new cases treated with diethyl stilbestrol are reported; 4 recovered. Placebos were given before the diethyl stilbestrol without effect.

The absence of a more uniform response to treatment is attributed to heterogeneity of the population studied with respect to psychosis, duration of psychosis, duration of hospitalization before treatment, age, and treatment.—*Author's summary.*

DANZIGER, L. AND H. ROBERT BLANK

Androgen therapy of agitated depressions in the male. *Med. Ann. of the District of Columbia* 9: 181. 1942.

Of 35 cases of probable involutional melancholia previously reported in the literature and treated with testosterone propionate, 21 recovered or improved markedly and 4 others improved temporarily. Five new cases are reported; two recovered and one showed marked improvement. Placebos given before the testosterone propionate were without effect.

The absence of a more uniform response to treatment is attributed to heterogeneity of the population studied with respect to psychosis.—*Author's summary.*

FREED, S. C., W. M. EISIN AND J. P. GREENHILL

The therapeutic efficiency of diethylstilbestrol esters. *J.A.M.A.* 119: 1412. 1942.

Diethylstilbestrol, diethylstilbestrol dipropionate and diethylstilbestrol dipalmitate were assayed for therapeutic potency in menopausal patients. Judging from the subjective responses diethylstilbestrol dipalmitate was the most active and had fewer undesirable side actions. The dosage used in all cases was equivalent to 5 mg. of the active component diethylstilbestrol.—C.C.P.

HAMILTON, J. B., R. I. DORFMAN AND G. R. HUBERT.

Androgenic and estrogenic substances in urine of eunuchoid and castrated men. Changes following administration of testosterone propionate. *J. Lab. Clin. Med.* 27: 917. 1942.

The average daily androgenic activity of the urine of 7 hypogonadal men was 18.8 I.U. (range 9.0 to 27) and that of 4 castrated men was 7.7 I.U. (range 3 to 11). The average daily estrogenic activity of the urine of the eunuchoids was 27.4 I.U. (range 8 to 50) and of the castrates 14.7 (range 5 to 28). These titers are lower than those found for normal young men; the range for the androgenic activity is from 22 to 132 I.U. and the range for the estrogenic activity is from 20 to 290 I.U. Daily injection of 20 mg. of testosterone propionate resulted in the elevation of the values for urinary androgenic activity to the range of normal young men. Urinary estrogenic activity was also increased as a result of conversion of testosterone to phenolic estrogenic substances. Upon the withdrawal of the testosterone the values dropped to the previous levels. In terms of molecular conversion to androgens and estrogens, the percentage recovery in the urine of the administered androgen is appreciable and comparable from person to person. Recovery following intramuscular injections in oil is less than that obtained upon implantation of pellets of testosterone propionate but is in turn greater than that occurring after oral administration. The literature pertaining to the biological assay of androgens and estrogens in castrated and eunuchoid men was reviewed and the values obtained by other investigators compared with those obtained in this study. 37 references.—C. P.

LATZ, L. J. AND EMIL REINER.

Further studies on the sterile and fertile periods in women. *Am. J. Obst. and Gynec.* 43: 74. 1942.

Statistical data from approximately 1000 written calendar records of over 11,000 menstrual cycles and approximately 50,000 sterile cohabitations compiled in chart form. This chart provides practical proof that ovulation occurs within a narrow time limit in the cycle, that the period of fertilization of the ovum is very short and that life span of sperm cells inside the female genital tract is not greater than 48 hours. Authors agree to the validity of the biologic law of sterility and fertility as originally propounded by Knaus and support its practicability.—*D.A.M.*

WALDBOTT, G. L. AND L. J. BAILEY.

Estrogenic hormone determinations in premenstrual asthma. *J. Allergy* 13, 125. 1942.

Blood estrogen content in 56 allergic women who presented a history of premenstrual aggravation of allergy was compared with 23 controls without such a history. In most patients the major diagnosis was bronchial asthma.

Blood used for estrogen assay was obtained between the second and fifth day before menstruation. Of the 56 patients with a history of premenstrual allergy, 35 exhibited negative, 5 a questionably positive, and 16 positive tests for estrogen. Of the 23 allergics without history of premenstrual allergy, 15 showed negative, 1 questionable, and 7 positive tests for estrogen. In a group of 42 non-allergic women with normal menstrual history, negative tests for estrogen were obtained in 2, questionably positive tests in 3, and positive tests in 37.

Thus, in the two groups of 79 allergic patients, 63 per cent gave a negative test for estrogen as contrasted with only 4.7 per cent recorded for the non-allergic controls.

Twenty-one unselected women with asthma and vasomotor rhinitis were given large doses (50,000 I.U.) of theelin from one to six times at one to three day intervals irrespective of the date of their menstruation without any effect of the allergic condition. Progesterone therapy was then tried in the same patients and it, likewise produced no improvement in the allergic condition.

Another group of 14 patients with perennial asthma, vasomotor rhinitis, and definite aggravation of symptoms premenstrually, was studied. Between two and eight doses of theelin and progesterone were given to these women within fourteen days before the expected onset of the menses. Since other therapeutic measures were simultaneously employed, it is difficult to draw conclusions concerning these cases, but it was felt that theelin was helpful at least temporarily in three patients.

Eight patients who had allergic symptoms only before the menses received above injection. Theelin was found to be of value in the control of symptoms in 2 of these patients and progesterone was helpful in 3 others.—*Author's summary.*

WESTBERG, V.

Histidinuria, a rapid method for the detection of pregnancy. *Acta. Obst. et Gynec. Scandina.* 21: 180. 1941.

Studies were made on specimens of urine of 680 women with intrauterine pregnancy, 11 with extrauterine pregnancy, 61 who had had an abortion, 238 non-pregnant women, 19 men with pulmonary tuberculosis and 3 with Cushing's syndrome. The histidine reaction was negative in 6% of women with normal pregnancy and negative in only 3% of women who were in the first 3 months of pregnancy. It was positive for all women with extrauterine pregnancy. The urine of nonpregnant women and of men gave positive reactions in 1.5% of the cases. Serial tests on 14 women in the puerperium showed that the secretion of histidine decreased rapidly after normal delivery. The same seemed true after induced abortion. Comparative mouse, rabbit and histidine tests for pregnancy in 171 cases showed that the histidine test can compete with the two former tests. The author used the method of Kapeller-Adler (cf. Wien. klin. Wochschr. 47: 168, 1934; C. A. 31: 3955) for the detection of histidine. —C. P.

WHITACRE, F. E., AND L. Y. FANG.

Fatty degeneration of the liver in pregnancy. Report of a case with recovery: chemical and histologic studies. *J. Am. Med. Assoc.* 118: 1358. 1942.

A case of fatty degeneration of the liver in pregnancy is fully described from the point of view of the biopsy findings as well as extensive chemical studies on the blood. The patient recovered. Early termination of pregnancy and immediate continued intravenous administration of glucose as well as liberal transfusions, are essential. It is believed that death results from hypoglycemia rather than from the extent of liver damage.—C. P.

HYPOPHYSIS

BUCHEM, F. S. P. VAN.

Cushing's disease. *Acta med. Scandinav.* 108: 544. 1941.

A patient showing the typical picture of Cushing's disease was observed for 8 years. There was localized osteoporosis of the spine and ribs, suggesting a hyperfunctioning parathyroid. At autopsy a typical basophilic cell adenoma of the hypophysis was found, the other glands being normal. Hyaline changes in the basophile cells were noted.—*F. R. Vanzant*, in *Biol. Abstracts.*

SALOMON, HUGO, AND JULIO CESAR LASCANO.

An extraordinary case of Simmonds' disease. *Semana méd.* 49: 746. 1942.

The patient, a man of 40, had a history of an ailment developing during 5 years. It started with nervous disturbances and pain in the joints, later gastrointestinal symptoms prevailed. At the time of first examination, a mild anemia, normal glucemia and a good tolerance to 10 units of insulin were observed. Free hydrochloric acid was absent in the gastric juice, the duodenal juice showed traces of trypsin, absence of diastase and considerable reduction of steapsin. Stools were liquid, gray and contained large quantities of fatty acids and soaps. A high calorie diet with 250 to 300 g. fat and 20 units of insulin daily kept the weight stationary without improving the symptoms. Cachexia developed gradually concomitantly with a voracious appetite and a B.M.R. of +31. The skin became dry and desquamated in large sheets. The patient developed delirium for a few days but clear consciousness returned preceding death. The pituitary showed diffuse sclerosis and two foci of ischemic necrosis without signs of inflammation. The number of chromophobes was diminished, to a less degree the eosinophils. Sclerosis of the adrenal cortex, atrophy of the thyroid and testes, amyloidosis of the spleen and lymphatic ganglia were considered to be secondary to the pituitary degeneration. The structure of the pancreas was essentially normal.—*A. E. M.*

SCHNEIDEWIND, ARTURO, AND SIMON TRAJTENBERG.

Generalized lentigo in a pituitary dwarf. *Semana méd.* 48: 1535. 1941.

A boy of 9 years is described whose growth had stopped almost completely when he was 4 years old. A year later there appeared pigmented spots on neck and face, which gradually spread over the thorax, abdomen, back and limbs but not over the mucosas. The face of the patient was characterized by a dry, rough and wrinkled skin. The hair was stringy with little pigment, the skull large and out of proportion with the face. Body size was 1.05 meters. The sella turcica was exceptionally small and the ossification of the bones retarded. The intelligence was normal.—*A. E. M.*

PANCREAS

HARTZ, P. H.

Routine staining of the beta cells of the islets of Langerhans with Masson's tetrachrome stain. *Arch. Path.* 33: 541. 1942.

The author described a method of routine staining of the beta cells of the islets of Langerhans with Masson's tetrachrome stain. Fixation of the material in a mixture of equal parts of Bouin's fluid and a saturated aqueous solution of mercury bichloride was suggested. The tissues were imbedded in paraffin and sections 6 microns thick were prepared wih the microtome. After removal of the mercury precipitate the sections were stained by the method of Larson and Levin (Arch. Path. 29: 272, 1940), the only difference being that fast green F. C. F. was substituted for light green. Beta cells appeared closely packed with red-staining granules and contrasted sharply with the other island cells, which showed a pale brownish color.—*E. von H.*

WOLF, WILLIAM.

Sensitivity to protamine zinc insulin. *Arch. Dermat. & Syph.* 45: 694. 1942.

A case of allergic reaction consisting in an itching eruption of the arms, dorsa of the hands and palms was reported following the administration of protamine zinc insulin. The diagnosis was confirmed by the intracutaneous injection of protamine zinc insulin, which produced a decided reaction within 3 minutes. Since neither protamine nor zinc are antigens, and since the true sensitivity to unmodified insulin is rare, the author explained the occurrence of this sensitization to insulin as a result of its delayed absorption due to the presence of protamine and zinc.—*E. von H.*

THYROID

CANTILO, ENRIQUE, AND CARLOS FERNANDEZ SPERONI.

Endocrinopathies VII. Filbrilloflutter in a severe thyotoxicosis. *Semana méd.* 49: 755. 1942.

A woman of 37 years originating from a region where goiter is endemic and having a history of mild goister developed severe cardiac symptoms of the following characteristics: apnea, auricular fibrillation, ventricular extrasystoles, dilatation of the cardiac area, pulmonary congestion. The electrocardiogram showed complex QRS waves with high voltage, flat T wave, complete arrhythmia. Arterial pressure 120/75. Orthostatic pulse 140. There was no loss in weight, the eyes were rather retracted in the orbits. It is pointed out that hyperthyroidism at the age of approaching menopause with a history of goiter is usually not of the Grave's disease type. The B.M.R. was +27 and 30, cholesterol 200 mg. The increase in blood sugar after 100 g of glucose was 122 mg. After thyroidectomy the pulse rate dropped to 75 and the arrhythmia disappeared. The E.K.G. became normal. —*A. E. M.*

COHN, A., AND S. E. FELDMAN.

The relation between the liver and the thyroid gland. I. Blood iodine as an indicator of liver function. *Am. J. Clin. Path.* 12: 27. 1942.

The influence of liver and gallbladder diseases on the blood iodine level was investigated. Iodine analyses were made by the method of Trevorrow and Fashena. Liver damage was produced experimentally in rabbits with carbon tetrachloride inhalations. It was found that liver and gallbladder disease did not elevate the blood iodine and that the functional relationship between liver and thyroid could not be expressed by the blood iodine level. —*E. von H.*

MARINE, DAVID, AND SAMUEL H. ROSEN.

Urinary excretion of capon comb growth-promoting substances in Graves' disease and myxedema and modification following iodine and desiccated thyroid therapy. *J. Mt. Sinai Hosp.* 8: 811. 1942.

Androgenic substances extracted from the urine by the method of Dingemanse, et al. were determined by the Fussgänger modification of the capon comb test. Administration of large amounts of iodine usually depressed the urinary androgen excretion in true Graves' disease, particularly if there was other evidence of clinical improvement, but not in non-Graves' patients. Desiccated thyroid administration to the point of elevating the basal metabolic rate did not definitely lower the amount of androgen excreted in non-myxedema patients but caused a significant rise in the 2 cases of myxedema of adults studied. In Graves' disease the absolute amount of androgen excreted in the urine varied widely; in some cases it was normal but more often was reduced. If the amount of androgen excreted is significant, it can only be a relative increase creating an imbalance in the realm of the steroid hormones. Possibly, one of the causes for improvement of patients with Graves' disease after partial thyroidectomy is that it aids in correcting such an imbalance. In myxedema of adults there appears to be an absolute decrease in the urinary excretion of androgen which may be raised by treatment with desiccated thyroid—*Ruth Berggren*, in *Chem. Abstracts.*

SILVER, SOLOMON, AND BORIS MAGASANIK.

The blood iodine in the period after thyroidectomy. Preliminary report. *J. Mt. Sinai Hosp.* 8: 1027. 1942.

Blood iodine (nondialyzable fraction) was elevated in all 7 cases of Graves' disease studied. Treatment with iodine tended to lower the blood iodine coincident with clinical improvement. The glood iodine underwent an average increase of 1.9 μg% immediately after thyroidectomy and returned to preoperative levels in 24 hrs. after completion of the operation in most cases. The 2 patients with the highest blood iodine values in the postoperative period were the same 2 who had the most unfavorable postoperative course.—*Ruth Berggren*, in *Chem. Abstracts.*